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DEFINITION OF OBJECTIVES, AND THE IMPORTANCE OF CONTROLS IN EVALUATING THE LOCAL USE OF SULFONAMIDES IN WOUNDS

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IT is comparatively easy to evaluate the influence of a chemotherapeutic agent on systemic or "medical" infections, in instances in which clinical response and mortality serve as reliable criteria. The problem of evaluating an agent in local therapy of wounds is infinitely more complicated. Testimony of this is the wide variety of agents and techniques employed in local wound therapy and the extent to which local management of infected wounds has become individualized. This "trial and error" therapeutics is likely to continue for a long time in the management of any condition in which so many variables are involved and in which, therefore, the specific objectives are beclouded.

There is apparently a widespread belief that the principal objective in the management of any infected wound is to destroy the bacteria in the wound exudates. Therefore, any agent which exercises a powerful antibacterial effect *in vitro* in the presence of animal protein has come to be looked upon as a potentially useful agent in shortening the healing time of the lesion through effective prevention or treatment of infection.

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However, the problem is not nearly so simple. In the first place, wounds differ greatly in respect to many variable factors. To list a few: (1) number, type and synergistic combinations of bacteria; (2) duration of the wound, i.e. how much time has elapsed between the initial injury and the development of the specific condition which it is hoped to treat effectively. This is related to (3) the "healing capacity" of the individual, which in turn is conditioned by many variables, in which age, vascularity, nutritional condition, and type of tissue are concerned. Furthermore, in established infections there are additional factors of (4) the anatomical extent of bacterial invasion; (5) the amount of necrosis; and (6) the immune reactions of the patient. When a wound treated with a certain type of antibacterial agent happens to heal with unanticipated rapidity, the observer naturally attributes the result to the local action of the drug on the bacteria; however, the true explanation of the result may be quite otherwise. For example, can anyone yet say whether the successful result of dakinization of wounds is due to its primary or secondary antibacterial action, its mechanical cleansing effect, its ability to promote dissolution of dead tissue, or to its "exosmotic" action on

the flow of tissue fluids into the wound? If all four effects are important, which one is dominant?

Some of these questions, undoubtedly, could be answered if it were possible to reproduce in animals the types of wound infections which are encountered in man so that controls might be employed. Certain experimental procedures have been utilized to investigate a few phases of the problem and the results probably constitute the most reliable data now available, but it must be recognized that no one experimental system can answer the question of, say, the treatment of choice for a carbuncle on the back of a man's neck.

Confusion in clinical research on sulfonamides has been further compounded because of the rapid succession of new drugs which have been introduced, the diversity of physical forms, vehicles, doses, and time schedules in which they have been employed, and, fundamentally, to a failure to recognize the limitations of local sulfonamide therapy. Dr. Frank Meleney has recently published a preliminary report of a comprehensive controlled investigation of the value of systemic and local sulfonamides in the prevention of local wound infection in accidental wounds and burns, a project of the Subcommittee on Surgical Infections of the National Research Council. After Pearl Harbor there was little doubt in the minds of some of us associated in this study but that prophylactic sulfonamides would both reduce the mortality from infection in war wounds, and also permit uncomplicated healing of most penetrating wounds subjected to débridement and closure within a reasonable time after injury. Consequently, it was a distinct surprise finally to discover that the frequency of *local* wound infections was actually somewhat higher in wounds treated locally and systemically by sulfonamides than in control wounds receiving no drug at all by either route. The frequency and severity of local infections were largely influenced by the balance of the factors which relate to wound healing *per se*, but not at all by our efforts to control the growth of bacteria in the wounds by implantation of sulfonamides before closure. We shall have occasion to return to this study later on, but at this time I wish only to use this passing reference to one specific study in order to complete the introduction of two cardinal facts about clinical research on local chemotherapy:

1. Every agent should first be evaluated in terms of the specific objective which it is supposed to achieve rather than in general terms, e.g.: "Does it provide bacteriostasis against a certain organism in wounds?" or "Does it delay healing of simple clean wounds?" Not: "Does it produce unexpectedly rapid healing of infected wounds in general?" After all, healing is the integrated outcome of many phenomena, particularly if the wound is infected, and the rôle of the agent under test must be assessed in specific terms.

2. It is essential to use controls, particularly those which will evaluate the vehicle in which the supposedly active agent is being employed, and which will determine the significance of the physical conditions to which the wound is being subjected, i.e. dryness, moisture, osmotic effect, *p*H, foreign body reaction, etc.

It may be exceedingly difficult, and at times even impractical, to meet these two criteria of sound research, but unless this is possible, the present deplorable state of confusion must inevitably continue and the improvement in our methods will be regrettably delayed.

For several years this department has been interested in certain fundamental considerations relating to the healing of infected wounds. One of the most thought-provoking chapters in this series of studies was written by Dr. David P. Anderson, who compared the healing curves of infected wounds, calculated according to the standard formula of DuNouy and based on daily changes in area and volume. The effect of various antiseptic dressings was measured by daily counts of bacteria in the wounds. Through this carefully controlled procedure, Anderson was able to conclude that drained infected wounds healed at the same rate as clean wounds provided invasive infection and slough were not present. Antiseptics such as azochloramid frequently induced sharp reductions in bacterial counts but failed in so doing to accelerate wound repair to any appreciable extent. It was finally

concluded: "In the management of infected wounds, less attention should be given to the selection of a potent local antiseptic agent. It is of more importance to consider the problem of increasing local tissue immunity, which may be influenced by factors of a general nature remote from the site of the wound, and aiding the sequestration of necrotic tissues rich in bacteria by mechanical or chemical débridement and adequate surgical drainage."

Although Anderson included sulfanilamide solution among his series of antiseptic agents, he did not employ sulfonamide powders or ointments. We may now re-examine some of the recorded experience with the topical use of sulfonamides in infected wounds in order to determine whether these agents impose a new and more favorable set of conditions for topical wound therapy.

TYPES OF CONTAMINATION

In order to systematize this discussion we should consider the local use of sulfonamides in the following types of contaminated or infected wounds:

1. Fresh contaminated accidental wounds, just after injury.
2. Contaminated accidental wounds many hours old, but not treated surgically.
3. Contaminated wounds which have been débrided or "trimmed" and left unsutured, possibly in anticipation of secondary suture.
4. Wounds similar to the preceding category but closed primarily, with or without tension.
5. Wounds displaying invasive cellulitis without slough.
6. Wounds containing slough and deep cellulitis.
7. Granulating wounds displaying only superficial surface infection.

Definitions. A contaminated wound is one in which the implanted bacteria have not yet commenced to multiply and produce toxins. An infected wound may be defined as one in which death of tissue or increased morbidity occurs as a result of the activity of bacteria in the region of the wound. These definitions are deliberately phrased so as to provide for an intermediate category of saprophytic lesions, in which bacteria are proliferating in surface fluids or in tissues already deprived of their architectural integrity and blood supply, but without the bacteria actually aggravating tissue loss or contributing to increased morbidity. Obviously the border lines between these three types of wounds are quite hazy and differentiation may at times be impossible.

1. *Fresh contaminated wounds just after injury.* The objectives in the *first aid* management of these wounds are to prevent additional contamination, particularly by airborne and droplet-borne pathogens from respiratory tracts of human carriers, to provide immobilization during transport of the patient and to prevent or at least delay the proliferation of bacteria already present in the wound. Here the conditions are, if ever, suited to effective utilization of local sulfonamides.

It is theoretically possible to prevent or modify the growth activity of most of the pathogenic species, particularly since the numbers are comparatively small, and the liberation of specific inhibitors from damaged tissue will not yet have commenced. Furthermore, there is no well established barrier between the bacteria and the drug, which, as shown by Hawking (7), will tend rapidly to diffuse throughout the surface of the wound. Questions of possible interference with wound healing do not intrude, because the period concerned usually spans only a few hours, during transportation of the casualty to a surgical theater. The value of applying sulfonamides to wounds immediately after contamination has been amply supported by a number of experimental studies in animals, including those of Nitti, Reed and Orr, Caldwell and Cox, and Hawking (7).

This is the altogether rational background for the widespread utilization of immediate prophylactic administration of sulfonamides to wounded soldiers. In our Army and Navy the current practice calls for the administration of 4.0 grams of sulfadiazine by mouth, and the application to the wound itself of 5.0 grams of sulfanilamide, both to be repeated after an interval of time at the discretion of a medical officer. The recommendation of sulfanilamide as the drug of choice for local use, by the Committee on Chemotherapeutics and

Other Agents, was based upon the higher solubility and diffusibility of this drug, and its freedom from deleterious effect upon wound repair. It was believed that these considerations more than outweighed the demonstrably greater antibacterial effectiveness of the less soluble drugs such as sulfathiazole and sulfadiazine, particularly during the first 24 hours after injury. Even after many months of warfare it is difficult to assess the true value of prophylactic sulfonamides used in this way. Some reports suggest that patients treated with sulfonamides actually reach base hospitals in much better shape than could have been expected under former conditions, but there are many opinions to dispute this contention and other factors in first aid treatment, such as plasma, may account for the improvement. In our civilian experience most patients reach the operating room within 3 hours of injury so that this question can be answered only by studies on war casualties, and controlled observations have not yet been published. The most that can honestly be said for prophylactic sulfonamide in wounded soldiers is that the practice is entirely rational, and that no evidence has been brought forward to contraindicate its use. Therefore, in the opinion of the writer there is every reason to continue the practice. The efforts of various workers to develop improved forms of the drug and vehicles for its slow liberation should be given every encouragement. An interesting example of progress along this line is the work of Hare and Clark, of Toronto, who recommend methyl cellulose as a solvent for sulfonamides when applied to contaminated open wounds. A combination of 30 per cent sulfathiazole and 70 per cent methyl cellulose implanted in the powdered state into open wounds will continue to liberate the drug over a period of several days, but of course must be completely removed from the wound before closure is carried out.

2. *Accidental wounds more than twelve hours old but as yet untreated.* Here again all considerations of reason would support the wisdom of introducing into the wound any drug which might check the already active proliferation of contaminating bacteria. The use of the drug may help to prevent invasion of tissue planes on the verge of suffering irreversible damage through infection. The production of certain proteolytic or "aggressive" toxins may be suppressed through the bacteriostatic action of the sulfonamide. Obviously the drug effect will be less pronounced on wounds of this type than on fresh wounds, nevertheless, one may still recommend that they be used. Almost certainly they will do no harm. If extensive contamination with anaerobes has occurred the usefulness of local sulfonamides is definitely open to question, particularly if putrid saprophytic infection has developed.

Wounds of the latter type are comparatively rare in civilian life but have been described by J. D. MacLennan as having been not infrequent among casualties in the Middle East. The predisposing factors are (1) the presence of a lacerated wound, (2) delay in surgical treatment, and (3) contamination with one or more types of clostridia—usually the proteolytic and pathogenic varieties.

In wounds in which contamination has proceeded to this degree, it seems most unlikely that the employment of local sulfonamide applications would exercise much influence on the healing of the wounds. The specific objectives should be to hasten the separation of slough by surgical or chemical methods, and to prevent invasive infection by means of systemic chemotherapy and serum therapy and immobilization of the wounded part. Since sulfonamide-inhibiting products of proteolytic degradation are present in abundance in such wounds the already limited action of sulfonamides against clostridia and other anaerobes would be quite ineffective even in *preventing* the development of putrid surface contamination of this type, if the other predisposing factors happen to exist.

3. *Contaminated wounds which have been débrided or "trimmed" and left unsutured (possibly in anticipation of secondary suture).* Because of the well-founded prejudice against primary closure of battle wounds it is certain that most war wounds will ultimately fall into this category. After surgical treatment the dressing will consist usually of tamponade with vasoline-impregnated gauze or plain gauze, supported either by an immobilizing splint or plaster cast. The incidence of serious

invasive infection in wounds so treated is generally thought to be quite low. In the series of civilian wounds studied in the National Research Council project previously referred to (Meleney), the incidence of serious *local* infection in soft part wounds débrided and left open was only 1.8 per cent. Although the corresponding figure for compound fractures left open was 16.5 per cent, a difference partly attributable to the greater damage to tissue in the latter cases, the *mortality* from infection was only 0.34 per cent in the combined group. The experience of Trueta was to the effect that gas gangrene and lethal infection occurred in only a fraction of one per cent of major compound fractures treated by débridement and plaster encasement. Therefore, the major question here is whether or not local sulfonamide will hasten the healing time of the wounds and shorten convalescence, either through minimizing bacterial interference on wound repair, or through permitting early secondary suture of certain of these wounds. If the wound is to be immobilized in dressing or plaster for a period of many days it is doubtful that the presence of any reasonable quantity of sulfonamide initially will provide an effect of sufficiently long duration to do more than delay bacterial proliferation. If the drug is reapplied every day or two the necessity for repeated dressing and exposure of the wound may well offset any possible advantage which the drug might offer. Here again, it can only be said that experimental and clinical data are not yet available to provide conclusive evidence of the value of local sulfonamide therapy in open wounds which have been subjected to good surgical care. The most important therapeutic considerations after débridement appear to be: (1) complete immobilization to permit establishment of barriers between traumatized and untraumatized tissues, and (2) performance of secondary suture or skin-graft as soon as the danger of invasive infection has passed, perhaps only after 4 or 5 days have elapsed.

4. Contaminated wounds which have been débrided or "trimmed" and closed primarily, with or without tension. Because of the unanimity with which the practice of primary closure of wounds is condemned in military circles, it may be agreed that this is not a military problem. However, it is undoubtedly a problem of major importance in civilian surgery. There has been an increasing tendency for surgeons to undertake primary closure of traumatic wounds in most hospitals in the United States, and one explanation of this trend is the widespread faith which exists in the effectiveness of locally applied sulfonamides in preventing infections in such wounds. That this faith is based more upon impression than fact is indicated by the recent report of Meleney. In the series of wounds studied under the program of the Subcommittee on Surgical Infections, the incidence of serious infections in soft part wounds closed without local sulfonamide (303 cases) was 5.3 per cent. When sulfonamides were used both locally and systemically (339 cases) the incidence of infections was 5.6 per cent. With compound fractures the corresponding figure for control cases was 7.1 per cent (in 99 cases) and for sulfonamide treated wounds 10.1 per cent (227 cases). There is little comfort in these figures for the advocate of topical sulfonamides in closed contaminated wounds. There was virtually no problem of *mortality* among these patients. When serious infections did develop among even control cases they were always treated with sulfonamides, and, in fact, only 4 deaths from infection occurred among the first 1,500 cases studied including the burns. However, the incidence of complicated healing of the local wound was at least as high when sulfonamides were used as when they were not used. The types of local sulfonamide included sulfanilamide alone, equal parts of sulfanilamide and sulfadiazine, and, more recently, sulfathiazole. In most cases the amount used was 0.1 gram per square inch of wound surface, but smaller quantities were used in some instances. In analyzing this experience it is apparent that the types of wounds in which complicated wound repair would be expected, such as large wounds, those showing maximal injury to tissue or maximal contamination, and wounds closed under tension, tend also to become infected wounds; the use of sulfonamides, which at most produces a transient repressive action on bacterial growth, does not in any way modify the likelihood of infection

developing. Sulfonamides probably fail to influence the frequency of infections in closed wounds for two main reasons: (1) The conditions which make for delayed or complicated healing are the very ones in which sulfonamide action is least effective, due to presence of sulfonamide inhibitors from devitalized tissue; and (2) the presence of any foreign body in a closed wound tends to complicate the process of wound repair—even though the foreign body is a bacteriostatic agent, the danger of infection may to some extent be increased by its presence.

The influence of topical sulfonamide powder on the healing time of closed experimental wounds has recently been studied in our laboratory by Dr. Harold Zintel. Wounds treated locally with sulfanilamide showed development of tensile strength at exactly the same rate as control wounds. However, when the less soluble sulfonamides were used, including sulfadiazine and sulfathiazole in both microcrystalline and macrocrystalline forms, there was a marked retardation in healing time, particularly striking at the 8th day. It is very likely that such a delay in completion of the reparative process will more than outweigh in its consequences the possible beneficial action of local bacteriostasis. It should be emphasized that the interference on wound repair by sulfonamides may be minimized by the use of very small quantities of the drug, but one may now question the wisdom of using them at all in civilian wounds which can be débrided early and closed.

We have had forcefully emphasized to us the cardinal importance of the basic physiologic factors in treatment of wounds, namely removal of all irreversibly damaged tissue and foreign bodies, avoidance of tension in closure, and thorough immobilization of the wound during the reparative stage. These considerations remain of far greater importance in the prevention of infection in closed wounds than the employment of any topical antibacterial agents thus far available. If some agent could be found which would completely destroy all bacteria in the area of the wound then the incidence of infection in closed wounds might actually be lowered, but such an agent is not yet available.

5. Wounds displaying invasive cellulitis without slough. In these wounds the bacteria have become successfully adapted to the environment of the wound, and have not only multiplied, but have commenced to invade the tissues adjacent to the wound; either by direct bacterial invasion or liberation of toxins they have commenced to produce systemic manifestations of their presence in the wound. At the same time, the bacterial injury to the architecture of the wound surfaces has not yet become irreversible. Can an infection of this type be modified by the topical application of an antibacterial agent such as a sulfonamide? It seems hardly likely unless the infected area is first excised. The most important component of such an infection is the advancing margin of the process—well below the surface of the wound. Whatever the effect of the sulfonamides might be on the bacteria in the superficial wound exudate, they do not possess the capacity to penetrate deeply below the wound surface in high local concentration and halt the activity of bacteria below the level of the most superficial capillary layer. Hawking showed that the concentration of a sulfonamide from a wound depot was no higher at a depth of 2.0 millimeters below the surface than in the body tissues remote from the site of the wound (8). Therefore, the systemic administration of sulfonamides is most certainly called for in the invasive infections of this type but there is little if any rational basis for the topical use of the drugs. Furthermore, there is as yet no adequately controlled clinical experience which may be cited in support of the employment of sulfonamides in this category of infected wounds. Immobilization, elevation, induced hyperemia, free drainage, and systemic chemotherapy must provide the basic therapeutic defense against threatened rapidly spreading invasive infections from wounds of any type. The remarkably low incidence of fatal invasive infections among our soldiers must be attributed largely to the thoroughness with which these measures have been applied.

6. Wounds containing slough and deep invasive infection. Serious infections in this category may develop in inadequately débrided accidental wounds or in third degree

burns, but the most common prototype is the carbuncle, with the Staphylococcus aureus the usual causative organism. Such a lesion commences as a cellulitis which spreads until effective inflammatory localization is brought about by immunity or chemotherapy. A major consequence of the cellulitis is the occlusion of the vessels in the infected area by compression or thrombosis, so that death of skin and subcutaneous tissue occurs, followed by formation of slough, and finally, fluid pus. The surgeon may release tension and perhaps remove all or part of the dead tissue. The spread of the lesion may perhaps be reduced by administration of chemotherapeutic agents systemically. However, there does not yet seem to be any evidence whatever that the local use of sulfonamide drugs either before or after surgical drainage will exercise much influence on the course of the lesion, and, in view of the pathological characteristics of these wounds, none should be looked for.[1] Dressings which encourage drainage, separation of slough, and "exosmosis" are undoubtedly of value; the application of heat will raise local metabolism and thereby hasten the process of resolution (though the amount of necrosis may be increased through widening the differential between oxygen supply and demand); however, these measures are not directed specifically against the bacteria themselves. It would be most unfortunate if a misdirected faith in chemotherapeutic agents were to lead to the abandonment of those measures of treatment which are rooted in basic understanding of the inflammatory process.

7. Granulating wounds displaying only superficial surface infection. After slough has separated and invasive infection is under control the main objective in therapy is to obtain complete healing and epithelization as rapidly as possible. Such healing occurs both through contracture and through growth of epithelium from the periphery, but may be greatly accelerated by application of skin grafts. Therefore, the yardstick for measuring the usefulness of local sulfonamide in wounds at this stage is whether or not the net effect is to facilitate growth of epithelium. If it is true that the presence of some types of bacteria, particularly Group A hemolytic streptococci, interferes both with epithelization and with successful application of skin grafts then, from a purely bacteriologic viewpoint, the local use of sulfonamides against these susceptible varieties of organisms would seem to be entirely rational. According to Colebrook and Francis the use of sulfonamides locally in granulating burns infected with streptococci has been eminently successful in causing disappearance of susceptible strains, and the same results could probably be obtained on other types of open granulating wounds. At the same time, one must guard against using the drug in a form which is ill-adapted to encouragement of wound healing. For example, the application of a sulfonamide preparation which tends to dry out, cake, and mechanically injure the new growth of epithelium, or one which causes the formation of edematous exuberant granulation, might gain on the bacterial front but lose the campaign in other sectors. Also, as has been emphasized by Gurd, Ackman, Gerrie, and Pritchard, one must be assured that the sulfonamide is available in an effective concentration in the aqueous phase, and yet not absorbed so rapidly by the body as to preclude its use on large areas through danger of excessive absorption. The development of the ideal vehicle for application of sulfonamide, the choice of the particular drug to be used and the factors of time and concentration required for optimum results provide an important subject for further intensive laboratory and clinical research. However, there is great need for *control* of this investigation at every turn, so that when the evidence is finally accumulated there will be general acceptance of the conclusions. Furthermore, it would be desirable to obtain further evidence that the presence of a purely *surface* contamination of a granulating wound with pathogenic bacteria is a significant factor in delaying wound repair. Anderson's data failed to indicate that such was the case.

I do not believe that we would be greatly handicapped in the treatment of open granulating wounds if sulfonamides were not avail-

[1] Penicillin appears to be far superior to sulfonamides as an antibacterial agent for topical use in infected wounds. This drug is not inhibited by products of tissue breakdown. Impressive results of local penicillin therapy as an adjunct to surgery in a controlled study of hand infections have been reported by Florey and Williams, *Lancet*, 1944, 1: 73.

able. Other methods of preparation of the wound, including zinc peroxide, Dakin's solution, and azochloramid, have all been used with success in our hands, and it seems possible that with each of these agents the antibacterial effect is of less importance than the effect of the treatment on the architecture of the granulating bed.

Local sulfonamide therapy of burns. Because of the increasing importance of burns in both military and civilian life the war years have been accompanied by an intensive re-examination of the whole problem of burn management. Certain fundamental advances have come through the growing recognition of the fact that burns are extensive open wounds and should be treated as such; namely, by protective dressings and immobilization. The use of coagulating chemicals which add further injury to the burned tissue, block drainage, render infection more serious when it occurs, and perhaps aggravate toxemia, is rapidly falling into disrepute. This is partly because the availability of large quantities of blood plasma has now made it possible to deal effectively with the major factor of plasma loss, in which tanning methods were thought to be especially helpful. Reports from medical officers in the Middle East and elsewhere are almost unanimous in condemning the practice of tanning burns in forward areas, where treatment must be initiated before the casualty is transported.

Early in 1942 Allen and Koch reported on a three year experience with the use of careful cleansing, and nonadherent splinted compression dressings, and courageously declared that the tannic acid treatment was outmoded. The basic principles advanced by these authors have now received wide support. One question which has not been answered with finality is whether sulfonamide should be incorporated in the compression dressing. The series of cases reported by Gurd, Ackman, Gerrie and Pritchard, of Montreal, is a testimony to what can be accomplished through sound planning and teamwork in burn management and the use of heavily padded compression dressings. The treatment of 100 major burns of over 20 per cent of body surface with only 6 deaths (all over 35 per cent) demonstrates what can be expected from such a regimen. However, in view of the results obtained by Allen and Koch the question may properly be raised as to whether the results of the Montreal group might have been equally good had the emulsion which they used contained no sulfonamide. We may all agree that the provision of a low systemic blood level of sulfonamide during the first few days after a burn probably helps to reduce the likelihood of invasive streptococcic or staphylococcic infection. However, so many factors combine together to reduce the effectiveness of sulfonamides in the presence of necrotic burned tissue as to rule out an *a priori* acceptance of the value of the local drug *per se*. In the series of cases from the co-operative project reported by Meleney, the use of compression dressings appeared to have a more important bearing on the reduction of infection than did the use of sulfonamides either generally or locally. Of the 347 cases included in Meleney's report only 2 patients died as a direct consequence of infection and each of these received sulfadiazine both locally and systemically. The value of local sulfonamides in burn therapy can be established beyond question only by a carefully controlled project, such as that which is now being carried out in Montreal, and we all await the outcome with keen interest.

SUMMARY

In directing his efforts to shorten the healing time of various types of contaminated and infected wounds, the surgeon must be realistic in selecting his tools to suit the principal *objectives* in each individual case. The maintenance of bacteriostatic conditions on the surface of the wound is the only objective which can reasonably justify the topical use of sulfonamides. This objective is limited in its importance in most established infections, and limited in its attainment through the use of sulfonamides because of the inhibitory effect of products of tissue breakdown on sulfonamide action. Priority should always be assigned to measures which achieve optimal conditions for wound healing, and direct antibacterial measures should usually take secondary position in local treatment. Systemic chemotherapy supplementing a form of topi-

cal therapy which is adapted to the local pathological condition will generally provide the best approach both to prevention and treatment. Local sulfonamide applications are probably useful in the first aid management of contaminated wounds between injury and definitive surgical treatment, and in preparing open granulating wounds for application of skin grafts, but are of little demonstrable value in the treatment of wound suppuration or invasive infection.

Definition of specific objectives and utilization of controls are essential features of any research, but are particularly indispensable to the evaluation of chemotherapeutic agents in local wound therapy.

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THYROID FUNCTION AS A FACTOR IN GALL-BLADDER DISEASE AND FORMATION OF GALL STONES

Clinical and Experimental Study

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A GREAT quantity of work has been carried out in recent years in an effort to find the cause of chronic gall-bladder disease; much still remains obscure. Most authors agree that the chronically infected gall bladder, with or without stones, as we commonly see it at the operating table, represents one of the final chapters in a long standing disease of the organ.

The pathogenesis of gall-bladder disease, both cholecystitis and cholelithiasis, was at first thought to be due entirely to infection. We have learned, however, that other factors, such as biliary stasis, the presence of pancreatic enzymes, hepatic insufficiency, and changes in the bile itself, must be considered. Most experimental work to date has attacked the problem as a purely local disease of the gall bladder and biliary passages. This study was undertaken to attack the problem as one of both a local and systemic nature, associated with a disease which affects body function generally, namely, hypothyroidism.

Our modern knowledge of cholecystitis began in 1890 with the work of Gilbert who advanced the infectious theory of the disease. Then followed the studies of Gilbert and Fournier, of Wilkie and Doubilet, of Phemister, Day, and Hastings, and of many others, most of whom studied the activity and reaction of the gall bladder in the presence of induced infection. The colloidal chemical theory of gall-stone formation was introduced by Aschoff in 1891. His work was followed and elaborated later by Aschoff and Bacmeister, Shade, Exner and Heyrowsky, and many others. Mentzer, Illingworth, Boyd, and others believe gall-stone formation is the result of difficulty in absorption of cholesterol by the gall-bladder wall. Graham and others advance the theory of supersaturation and precipitation of cholesterol occurring as the result of excretion of cholesterol by the gall-bladder wall. This process they believe is accentuated by infection.

With the accumulation of data, more and more evidence points to stasis as an important factor in this disease. Phemister, Aronsohn, and Pepinsky noted a change in the type of stone found, depending upon the degree of stasis present. Andrews, Dostal, and Hrdina reported that stasis is usually accompanied by infection, which in turn results in the absorption of bile salts by the gall-bladder wall.

A few authors have noticed pigment stones associated with stasis. Aronson produced pigment stones in two dogs after mechanically inducing partial common duct obstruction. Cole, Novak, and Hughes reported similar stones in two of their animals after partial obstruction of the cystic duct was produced. These animals in addition showed chronic inflammatory changes in the gall-bladder walls. Bisgard and Baker obstructed the common ducts of goats just distal to the entrance of the pancreatic ducts. This allowed pancreatic enzymes to enter the gall bladder. In three of the goats in which stasis had been prolonged, several small pigment stones were found in addition to evidences of chronic infection of the gall-bladder walls.

Most of the experimental work of the aforementioned authors and of many others has attacked the problem as an entirely local disease. Is there a deficiency disease which could affect gall-bladder function? Certainly, infection, stasis, and chemical changes occur, but is there some internal secretion, the lack of which would cause improper function of the gall bladder and thereby lower the resistance of the organ to infection and the associated

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changes we commonly find? With this in mind, and because hypothyroidism and cholecystitis have many common relationships, the effect of thyroid insufficiency on biliary function was selected for study.

Hertough in 1900 pointed out a possible relationship between these two diseases. Buttner and later Loranger again pointed out an existing relationship between these two diseases and decried the fact that no experimental work had been done on the problem.

Fortune, Brandon, Davis, Vis, Barksdale, Musser, Wharton, Lester, and many others have shown that mild degrees of hypothyroidism are frequently associated with the gastrointestinal symptoms commonly seen in cholecystitis. J. W. Hinton reviewed 43 cases of hypothyroidism which presented the typical symptoms of peptic ulcer. Riegel, Ravdin, and Morrison noted that thyroid disorders are frequently associated with gall-bladder disease.

It is of more than passing interest that all gall stones contain cholesterol. A high blood cholesterol level is found in both gall-bladder disease and hypothyroidism. Epstein and Lande, Gardner and Gainsborough, Hurxthal and others have noted an inverse relationship between thyroid function and the blood cholesterol level, and many believe that the blood cholesterol level is a more accurate index of thyroid function than the basal metabolic rate.

Both hypothyroidism and cholecystitis are much more common in females, and both diseases are associated with obesity. Almost any busy clinician can look back and remember patients with gall-bladder disease who presented the typical picture of hypothyroidism. This is especially true of women, whose thyroid is apt to become depleted during pregnancy and with the onset of the menopause, a time when gall stones often occur.

Basal metabolic rates were taken on 50 normal adults in this clinic. Two per cent of the patients had rates between +15 and +10; 36 per cent of the patients had rates between +10 and 0; 54 per cent of the patients had rates between 0 and −10; 4 per cent had rates between −10 and −15, and 4 per cent had rates below −15. Fifty consecutive cases of chronic cholecystitis were subjected to basal metabolic studies. Twenty-four per cent of these patients had rates between +10 and 0; 40 per cent had rates between 0 and −10; 22 per cent had rates between −10 and −15, and 14 per cent of the patients had rates below −15.

Blood cholesterol studies were done on the aforementioned series of 50 cases of chronic cholecystitis. These studies showed 33.7 per cent of the cases within normal limits; 18.4 per cent showed a high normal level (180 to 190 mgm. per cent), and 47.6 per cent showed a high blood cholesterol level (190 to 250 mgm. per cent). Cholesterol determinations were made according to the methods of Myers and Wardell, and all specimens were taken with patients fasting. Of 161 cases of chronic cholecystitis entering the hospital, 87.6 per cent were obese, 6.6 per cent slightly overweight, and 5.8 per cent normal or below.

We believe that these figures show a definite trend toward hypothyroidism in these patients. Bockus and Willard, in a similar study, found only 11.1 per cent of their patients had low basal rates, but 51 per cent of their patients showed a blood cholesterol level of over 200 milligrams per cent. They were also of the opinion that their patients showed evidences of thyroid dysfunction. Higgins has shown that marked symptoms of hypothyroidism are often seen with but moderate changes in the basal metabolic rate. In view of this, and also of the recent studies of Hinton, Musser, Seward, and others, the significance of the foregoing figures may be greater than one would expect.

EXPERIMENTAL STUDIES

The experimental approach to the problem was divided into a number of parts in order to determine: (a) the effect of a prolonged hypercholesterolemia, as induced by thyroidectomy, on the chemistry of the gall-bladder bile; (b) similarly to study the effect of thyroidectomy and induced hypothyroidism on biliary output and hepatic bile chemistry; (c) under similar conditions, the effect of a prolonged hypercholesterolemia on the gall bladder, and (d) gall-bladder function in these animals by means of cholecystograms.

TABLES I AND II.—CHEMICAL STUDIES ON GALL-BLADDER BILE TAKEN FROM NORMAL AND HYPOTHYROID DOGS

Table I.—Normal Dogs

Dog No.	Blood cholesterol*	Bile salts*	Bile cholesterol*	Ratio of bile salt to cholesterol	Duration of hypercholesterolemia—mos.
40–76	122.5	7045.5	61.2	122.5	
40–88	135	6015.5	63.6	113.1	
40–11	134	6657.6	53.4	132.2	
40–67	132.7	5613.3	58.6	101.2	
Average	131.0	6332.9	59.2	117.2	

Table II.—Hypothyroid Dogs

39–372	203.3	8871.8	57.5	173.9	2
40–5	193.6	7300.0	54.1	153.6	2
40–21	195.6	8470.0	53.9	157.6	2
40–27	194.4	7611.2	69.1	134.3	2.5
39–375	204.4	6478.1	58.4	138.7	3.5
39–371	185	8130.0	58.7	139.6	4
39–376	234.4	6436.3	53.2	128.6	3
Average	201.5	7613.0	57.8	146.6	2.64

*mgm. per 100 c.c.

A. Gall-bladder bile studies. The animals used throughout the period of experimentation were healthy dogs on a routine kennel ration. Blood cholesterol determinations were made on 4 animals according to the method of Myers and Wardell. The values ranged from 122 to 135 milligrams per cent, with an average of 131 milligrams per cent. The determinations were made at 3 day intervals throughout the period of experimentation.

Next a series of 7 dogs was subjected to total thyroidectomy. This was performed under barbital anesthesia, and special care was taken to preserve the parathyroid glands intact. The blood cholesterol levels in these animals and in control animals were determined every 3d day. The levels in the control and in the experimental animals remained within normal limits until the 27th to the 31st postoperative day, at which time the blood cholesterol values for the experimental animals rose to between 185 and 235 milligrams per cent, with an average of 201.3 milligrams per cent. From that period onward, the values for the thyroidectomized group remained high while the cholesterol values for the normal dogs remained within normal limits.

Gall-bladder bile samples were studied in both groups of animals. Bile samples were obtained through a right upper abdominal incision, made under sterile precautions. The gall bladder was aspirated with a fine needle, and then the abdominal wall was closed in layers. A sterile dressing was applied, and a canvas jacket was placed on the animal to prevent contamination of the operative site. This procedure was repeated weekly until 6 consecutive determinations were obtained in each of the normal and thyroidectomized dogs. Each sample was examined microscopically and cultured before chemical determinations were carried out. This is an important procedure because the presence of infection or of cells might induce error in deduction.

Tables I and II show the results obtained in the normal and thyroidectomized animals, respectively. The figures represent the average for a minimum of 6 consecutive samples on each animal. These studies, as before mentioned, were not carried out until each of the experimental animals had carried an elevated blood cholesterol for at least 2 months. Autopsies revealed normal appearing biliary system, liver and kidneys.

TABLE III.—HEPATIC BILE STUDIES IN NORMAL AND THYROIDECTOMIZED DOGS. ALL EXPERIMENTAL ANIMALS WERE ALLOWED TO CARRY A HIGH BLOOD CHOLESTEROL LEVEL FOR AT LEAST 1 MONTH PRIOR TO STUDY

Dog number	Daily output of bile in c.c.	Bile salts*	Cholesterol*	Ratio of bile salt to cholesterol	Daily output of bile salt in c.c.	Daily output of cholesterol in c.c.	Blood cholesterol*	Duration of hypercholesterolemia—mos.
Normal Animals								
40–2	203.3	1711.6	11.2	147.9	3494.8	22.4	135.5	
48–38	142.3	1490.3	10.7	145.6	2094.9	15	135	
39–330	193.7	1507.5	8.9	182.1	2755.4	16.8	143	
40–60	127	1562	9.7	162.3	1982.4	12.9	141.2	
39–318	164.1	1631.7	12.4	155.5	2166.6	17.6	137.4	
39–332	100	1259.6	10.8	121.1	1315.6	11.4	144.7	
Average	154.9	1527.1	10.6	151.4	2301.6	16.0	139.9	
Thyroidectomized Animals								
39–375	95	920	14.2	66.1	874	13.5	207	4.5
39–376	71.6	1074	10.6	97.3	726	7.5	207.3	1
39–269	182.3	979.6	13.9	88	1776	23.9	227.3	1
39–225	114.2	745.7	10.0	72.5	897.8	13.3	202.3	5
39–252	106.5	698.5	10.6	68.1	911.2	14.1	202	1.5
39–303	70.8	977.3	11.9	76.5	671.5	8.4	194.4	3.5
39–253	189.5	784.9	10.9	72.8	1535.1	22.9	202.5	1.5
39–271	128.3	853.3	10.2	57.4	771	12.1	208.5	4.5
39–224	51	875.4	10.9	65.6	356.5	5.4	206.5	5
Average	112.2	856.4	11.3	73.8	946.4	13.4	206.2	3.04

*mgm. per 100 c.c.

Examination of the tables will show that there is no significant difference between the control and experimental groups with respect to bile salts[1], bile cholesterol[2], and bile salt-cholesterol ratio. In both groups the bile salts-cholesterol ratio is far above the critical precipitation level of 13 suggested by Andrews and associates. It may be concluded from these data that hypothyroidism with an accompanying hypercholesterolemia existing over a period of 2.64 average months has no significant effect on the gall-bladder bile with respect to its bile salt, cholesterol content and bile salt-cholesterol ratio.

B. Hepatic bile chemistry. In order to study the chemical nature of hepatic bile, 6 normal and 12 thyroidectomized dogs were used. The blood cholesterol levels of the experimental animals varied from 200 to 230 milligrams per cent, while those of control animals varied between 130 and 150 milligrams per cent. Animals of approximate weight were used.

The experimental animals were allowed to carry a high blood cholesterol level for from 1 to 5 months; cholecystectomy was then performed, and the cystic duct was tied off. A small silver cannula was placed in the common duct, and a small rubber catheter was attached to it and brought out through the flank where it was attached to a large rubber balloon by means of a rubber cuff. The common duct was tied off distal to the silver cannula. By this arrangement hepatic bile would flow through the catheter and be collected in the balloon which served as a reservoir. A large soft sterile dressing was applied to the wound, external portion of the catheter, and the balloon. This was in turn covered by a large canvas jacket to prevent the animal from contaminating the area.

[1]Bile salts determined after method of McClure, Vance and Greene.
[2]Bile cholesterol determined after method of Elman and Taussig.

By this method the total daily bile output was collected, measured, and cultured. About 10 cubic centimeters of each daily sample was taken for study, and the remainder was fed back again to the animals through a stomach tube.

Each normal and experimental animal was studied for a period of 10 days and the average daily bile output in cubic centimeters, bile salt, and cholesterol content, bile salt-cholesterol ratio, daily bile salt and cholesterol output, and blood cholesterol levels were determined. The results are shown in Table III. Three of the experimental animals were discarded. One of the animals died of bile peritonitis and the other 2 showed clinical evidences of biliary infection and had positive bile cultures.

The blood cholesterol levels in the experimental animals remained high throughout the course of the experiments; however, in spite of this the bile cholesterol values remained within normal limits. The total daily output of cholesterol by comparison showed an insignificant change.

There was a notable difference in the total daily output of bile and also in the bile salt content of bile from thyroidectomized animals. The bile salt content was not inversely proportional to the daily output of bile. The bile salt-cholesterol ratio in the experimental dogs was 73.8, while in the normal dogs it was 151.4. This ratio of 73.8 is still far above the critical level for cholesterol precipitation (13) as described by Andrews and associates. Whether the ratio and bile salt content would fall still farther if the animals were allowed to remain in a hypothyroid state for a longer period of time (1 or 2 years), is a matter for further study. Four grains of thyroid extract were given daily to 3 of these animals, and after 6 to 8 days the total bile output and bile salt content rose to comparatively normal levels. This, however, was not considered significant in view of the small number of animals studied. Autopsies on all animals revealed normal biliary structures, liver, and kidneys.

C. Gall-bladder wall analysis. The gall-bladder walls were studied both microscopically and chemically to determine whether a prolonged hypercholesterolemia associated with the hypothyroid state would result in deposit of cholesterol within the gall-bladder wall. We were interested in finding out whether a condition simulating cholesterosis of the gall bladder could be produced experimentally.

Total thyroidectomy was performed on 10 normal dogs. After a period of hypercholesterolemia ranging from 2 to 5 months, the gall bladders of these animals were removed. The gall bladders of 7 normal animals were also removed and these were used as controls. Blood cholesterol levels of the normal animals varied from 127 milligrams per cent to 149 milligrams per cent; those of the experimental animals varied from 176 milligrams per cent to 230 milligrams per cent.

Small biopsy specimens were removed from each gall bladder and the remaining portions were washed with saline and dried to constant weight. The specimens were frozen and frozen sections were made. The sections were then stained according to the Schultz technique for demonstrating cholesterol. With this method cholesterol is stained a greenish hue which lasts about 1 hour. When these sections were examined microscopically, small concentrations of green pigment were noticed beneath the mucosa and submucosa. There appeared to be more of this deposit in the gall-bladder walls of the thyroidectomized dogs than in those of the normal controls.

The gall bladders were carefully washed with saline and dried to constant weight. The cholesterol was then extracted from them and a quantitative determination of the amount present was made. Tables IV and V show the values obtained for the normal and experimental animals. The average content of cholesterol in each gall-bladder wall per gram of dry weight specimen was 0.0132 milligram for the control group and 0.0101 milligram for the experimental group.

The smaller value for the experimental group cannot be taken to indicate that hypercholesterolemia causes a reduction in the cholesterol content of the gall-bladder wall since there is a normal variation. The results obtained from quantitative analysis of the gall-bladder walls must be considered more significant than the microscopic studies, since

TABLES IV AND V.—QUANTITATIVE CHEMICAL DETERMINATION OF CHOLESTEROL CONTAINED IN GALL-BLADDER WALLS OF NORMAL AND HYPOTHYROID DOGS

Table IV.—Normal Dogs

Dog number	Blood cholesterol	Dry weight specimen—gm.	Cholesterol content—mgm.	Cholesterol content per gram dry specimen—mgm.	Duration of hypercholesterolemia
40-61	134	.325	4.44	.0136	
39-221	127	.331	2.468	.0074	
39-346	143	.122	4.88	.0400	
40-28	135	.267	3.54	.0132	
40-79	143	.249	2.082	.0084	
40-60	149	.314	3.560	.0113	
40-2	137	.435	3.96	.0091	

Table V.—Hypothyroid Dogs

39-250	215	.185	2.1	.0113	3 mos.
39-27	202	.314	3.81	.0120	4 mos.
39-252	197.5	.312	4.0	.0126	2.5 mos.
39-262	176.0	.280	2.916	.01041	4 mos.
39-251	198.0	.981	8.88	.00905	3 mos. 6 days
39-224	198.0	.232	3.124	.0134	4 mos. 20 days
39-225	205.0	.164	1.940	.0118	4 mos. 25 days
39-262	179.5	.332	3.418	.01029	4 mos.
39-269	230	.336	4	.0019	2 mos. 2 days
39-226	186	.260	2.162	.0083	5 mos.

the latter method is subjective. The values as demonstrated show neither an absolute nor a relative significant increase in cholesterol content in the gall-bladder walls.

D. Studies on gall-bladder function. The most interesting and most significant findings in the entire study were noted while we were determining gall-bladder function in these animals. When thyroidectomized animals were operated upon, it was noticed that their gall bladders were almost always greatly distended. The bile contained in these gall bladders was found to be thick and viscid, and contained a large amount of thick brown precipitate. On transillumination of this bile, two definite layers appeared, as shown in Figure 1, an upper layer of clear yellow bile, and a heavier layer of black viscid material. In Figure 2 the bile alone is transilluminated. The two definite layers are easily distinguished. The thick sediment which contains numerous particles of pigment is illustrated also in Figure 3.

The gall bladders of 5 of the animals contained numerous small, black, friable concretions in addition to a large amount of viscid material. Figure 4 shows the concretions found in 4 of the dogs; the 5th was inadvertently not photographed. The concretions were analyzed by Dr. R. F. Hanzal of the department of biochemistry and were found to be composed of a trace of calcium and cholesterol, but were for the most part composed of pigment and polymerized pigment soaps.

Concretions and precipitates such as the above have been previously noted after a prolonged period of biliary stasis. Aronson, Bisgard, and Baker, and Cole, Novak, and Hughes reported similar stones after mechanically induced experimental biliary obstruction of a partial type. In our experimental animals the gall bladders and biliary systems had been disturbed in no direct way. Thyroidectomy had been performed from 2 to 5 months previously, and the concretions and

TABLE VI.—RECORD OF GALL-BLADDER FUNCTION IN THYROIDECTOMIZED DOGS

Dog number	Total thyroidectomy	Blood cholesterol	Duration of elevation of blood cholesterol	Cholecystograms 4–13–40	Repeat cholecystograms 4–30–40	Thyroid extract gr. 4 q.d. started	Blood cholesterol 5–28–40	Cholecystograms 6–4–40 after thyroid administration	Thyroid extract stopped	Blood cholesterol 40 days later	Total days thyroid given
Group I											
39–371	12–12–39	187	3 mos. 20 days	P. 12 hr.	Failed	5–13–40	117.5	N. Emptied 1.5 hr.	6–5–40	161.7	23
40–25	1–16–40	198	2 mos.	P. 8 hr.	Failed	5–13–40	159.5	N. Prolonged 6 hr.	6–5–40	203	23
40–21	1–12–40	194	3 mos. 20 days	P. 12 hr.	Failed	5–13–40	137.2	N. Emptied 3 hr.	6–5–40	212	23
40–5	1– 8–40	195	3 mos.	P. 8 hr.	P. 8 hr.	5–13–40	147.2	Sl. Prol. 6 hr.	6–5–40	195	23
40–13	1–10–40	197	3 mos. 19 days	Failed	Failed	5–13–40	123	Sl. Prol. 6 hr.	6–5–40	172.1	23
Group II											
40–15	1–10–40	220	4 mos. 18 days	Failed	Failed	Control	197.2	Failed	Control	185	—
30–194	8– 8–39	210	9 mos. 18 days	Failed	Failed	Control	182	Failed	Control	180.6	—
40–6	1– 8–40	255	3 mos.	P. 24 hr.	Failed	Control	258	Failed	Control	192	—
40–48	2–27–40	235	18 days	P. 12 hr.	N. 3 hr.	Control	235	Prol. 72 hr.	Control	207	—
Group III (Control)											
Stock	Normal	135	Normal	—	N. 3 hr.	Control	—	Control normal emptying 3 hr.	Control	145	—
Stock	Normal	139	Normal	—	N. 3 hr.	Control	—	Control normal emptying 3 hr.	Control	151	—
Stock	Normal	142.5	Normal	—	N. 3 hr.	Control	—	Control normal emptying 5 hr.	Control	147	—
Stock	Normal	127	Normal	—	N. 3 hr.	Control	—	Control normal emptying 3 hr.	Control	132	—
Stock	Normal	131	Normal	—	N. 1.5 hr.	Control	—	Control normal emptying 4 hr.	Control	142	—

F.—Gall bladder failed to visualize.
P.—Gall bladder emptying time prolonged.
N.—Normal emptying time.

previously mentioned precipitates were noted when the abdomens of these were first opened in the process of study connected with biliary chemistry. Similar precipitates and stones were not found in the control animals. In view of the large amount of precipitate found in almost every one of our experimental animals, which had been thyroidectomized for a period of 2 months or more, we believe the factor of biliary stasis deserved further investigation.

Cholecystograms, with careful emptying time studies, were made in an effort to determine the power of the gall bladder to concentrate the dye and also the degree of stasis present. The average emptying time for normal animals was compared to that of the experimental animals receiving the same dose of dye. Fifteen normal dogs were used in the study. Ten normal dogs were thyroidectomized while the remaining 5 dogs were used as controls. All animals were placed on the same routine kennel ration. Table VI shows graphically the progression and results of the study. One of the dogs died after thyroidectomy and is not shown in the table.

In all 9 of the experimental animals a hypercholesterolemia developed, which varied from 187 to 255 milligrams per cent for the experimental animals as compared to a variation of from 135 to 142 milligrams per cent for the controls. Hypothyroid dogs were allowed to progress for periods varying from 18 days to 9 months and 18 days before further studies were attempted.

Cholecystograms were made in the following manner: Intravenous tetraiodophenolphthalein (Mallinckrodt), 50 milligrams per

Fig. 1.

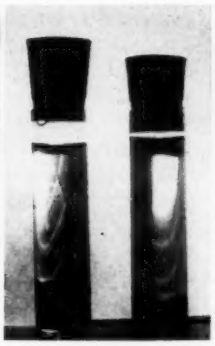

Fig. 2.

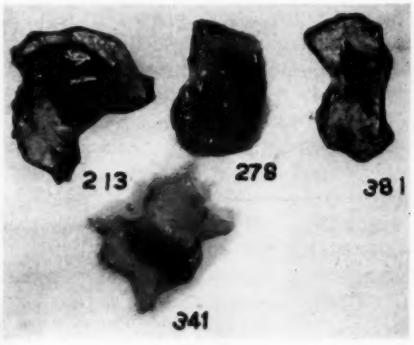

Fig. 3.

Fig. 1. Gall bladder transilluminated to show heavy precipitate.

Fig. 2. Gall-bladder bile showing heavy sediment.

Fig. 3. Several gall bladders which have been removed from hypothyroid dogs. These specimens show pigment precipitate.

kilogram of body weight, was mixed with 250 cubic centimeters of normal sterile saline and given to each animal at 6:00 p.m. on the evening prior to x-ray studies. The animal was then kept fasting and the first roentgenogram was taken at 9:00 the following morning. The animals were then each given 1 pint of heavy cream and a second roentgenogram was taken one-half hour after the first. Succeeding x-ray pictures were taken at intervals of 1½, 3, 6, 12, 24, 48, and 72 hours except in unusual cases when they were taken more frequently. All plates were interpreted by Dr. Thomas Knickerbocker of University Hospitals' x-ray department, who rendered invaluable assistance during this study.

A number of stock animals were studied and in each an excellent visualization of the gall bladder was obtained. In each of the normal dogs the shadow had decreased markedly in size and density 1½ hours after feeding. Within 3 to 5 hours after feeding the gall-bladder shadow had entirely disappeared or remained only faintly visible. Results in 5 normal dogs studied are shown in Table VI.

By means of the same technique 9 thyroidectomized dogs were studied. In 3 of the animals no shadow was obtained. In the remaining 5 animals a fairly good shadow was obtained. Two of these animals showed an emptying time of 8 hours, 3 animals emptied in 12 hours, and 1 animal in 24 hours. In each of these 6 animals the shadow after 3 to 5 hours was of the same size and intensity as it was prior to feeding, and in succeeding plates decreased in intensity but not in size.

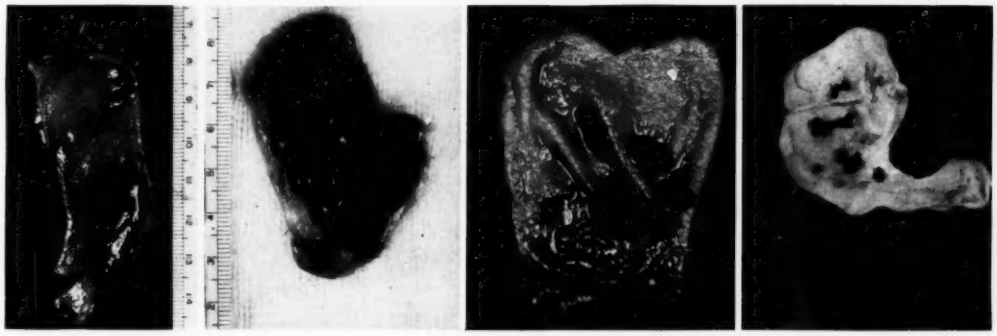

Fig. 4. Four gall bladders removed from hypothyroid dogs. The specimens show concretions and heavy precipitate.

Because of the marked difference in results obtained between the thyroidectomized and normal animals, the entire roentgenographic study was repeated 2 weeks later, the same animals and the same technique being used. In this study there was less evidence of good gall-bladder function than in the first. In 7 experimental animals no gall-bladder shadow was obtained. One animal showed a normal visualization and emptying time. Incidentally the latter animal had been thyroidectomized a much shorter period of time, approximately 2 months. Three of the animals failed to show a gall-bladder shadow in both studies.

The animals shown in Table VI were divided into 3 groups. Groups I and II included the experimental animals and Group III was composed entirely of normal control animals. Five of the experimental animals in Group I were given thyroid extract, 4 grains per day, for 23 days. Animals in Group II were allowed to continue in a hypothyroid state. Blood cholesterol levels were carefully determined on all dogs. The animals in Group I showed a return to normal, as shown by their blood cholesterol levels, in approximately 23 days. The levels which had formerly been high (187 to 198 mgm. per cent) now varied between 117.5 and 159.5 milligrams per cent after administration of thyroid extract. In Group II, animals not receiving thyroid extract, cholesterol levels remained high, varying between 182 and 258 milligrams per cent. Control animals were within normal limits.

Cholecystograms were again repeated to determine whether administration of thyroid extract in animals in Group I would have any effect on the x-ray results in that group as compared to the animals in Group II, not receiving thyroid extract. The same technique as previously described was used.

A marked improvement in results was obtained. Every animal in Group I showed a good visualization of the gall bladder. Two animals showed a rapid disappearance of the gall-bladder shadow after feeding, while the remaining 3 showed only a slight prolongation of the emptying time and were considered within the limits of normal.

In the group not receiving thyroid extract, we were unable to obtain visualization of the gall bladder in 3 of the animals. In the 4th animal, excellent visualization was obtained, but little change in intensity or size of the shadow was noted for 72 hours in spite of frequent feedings. Normal animals showed normal function and visualization. Thyroid extract was discontinued in the animals in Group I and a hypercholesterolemia developed, varying between 161.7 and 212 milligrams per cent. Autopsies were carried out on all the animals. The gall bladders of the experimental dogs showed a large amount of precipitate, but no signs of inflammation were noted. Microscopic sections of the liver, gall bladder, kidneys, and great vessels were normal in appearance.

In reviewing the complete x-ray studies, it may be concluded that thyroid extract or a normal functioning thyroid gland is essential for normal gall-bladder activity. The results in Group I were much improved after the administration of thyroid extract. Graham reported in 1925 that visualization of the gall bladder could almost always be expected if the organ was functioning normally. Many normal animals were examined in addition to those listed in the table and all gall bladders visualized normally. It appeared that the longer an animal progressed after thyroidectomy, the poorer his gall-bladder function became. In one animal which had been thyroidectomized 4½ months previously and in another which had been thyroidectomized 9½ months previously, the gall bladders failed to visualize on 3 successive occasions. The degree of hypercholesterolemia seemed to have little effect on visualization or emptying time in animals not receiving thyroid extract.

SUMMARY

We have attempted to determine clinically and experimentally whether a relationship between gall-bladder disease and hypothyroidism exists. Clinically the two diseases have aspects in common. Both are more common in middle aged females and are similarly associated with obesity. Digestive complaints, such as nausea, epigastric pain, constipation, etc., are frequently associated with both hypothyroidism and chronic cholecystitis. High blood cholesterol levels are seen in both dis-

eases. In this clinic 36 per cent of patients with chronic gall-bladder disease showed basal metabolic rates of −10 or below, and an additional 40 per cent showed a basal metabolic rate from 0 to −10. Only 24 per cent showed a positive metabolic rate. This, we believe, is a definite trend toward hypothyroidism in these patients as compared to normal individuals.

A sustained elevation of the blood cholesterol occurred in thyroidectomized dogs, appearing about 27 to 30 days following operation. A prolonged high blood cholesterol level (2 months or more) did not result in an increase in the cholesterol output in the hepatic bile. The hepatic bile salt content and total biliary output were somewhat low in these animals as compared to the normal. Gall-bladder bile aspirated from the gall bladders of hypothyroid dogs showed a normal bile salt and cholesterol content in spite of the fact that an elevated blood cholesterol existed.

Gall-bladder walls in hypothyroid dogs were studied microscopically and clinically for cholesterol deposit within them. No significant difference from the normal was found.

A most striking finding was noticed when the abdomens of the hypothyroid animals were first opened. The gall bladders of most all the hypothyroid animals were greatly distended and contained much thick brown precipitate. In 5 of the animals many concretions of various sizes were found. Chemically these concretions were composed of pigment, pigment soaps, and traces of calcium and cholesterol. Such findings have been seen previously in dogs after mechanically induced stasis.

Several dogs were thyroidectomized and cholecystograms were made. As shown in Table VI, the gall bladders of the experimental animals either failed to visualize, or, after visualization, showed a prolonged emptying time as compared to the normal. In 5 of these thyroidectomized animals thyroid extract, 4 grains per day, was administered for 23 days, after which cholecystograms were repeated, and all animals receiving thyroid extract showed normal visualization and function of their gall bladders.

CONCLUSIONS

It may be concluded that the hypothyroid state does materially affect gall-bladder function. The large quantity of débris and concretions found, plus the x-ray findings, indicate that a marked degree of stasis takes place within the gall bladder. Apparently a high blood cholesterol, as indicated by the hypothyroid state, does not result in an increase in the cholesterol content of the hepatic bile, nor does it result in a deposit of cholesterol within the gall-bladder walls. Autopsy findings in all these animals revealed normal appearing gall-bladder walls, liver, kidneys, and great vessels.

Obviously infection plays a major part in the production of cholecystitis and cholelithiasis. However, any constitutional disease which impairs gall-bladder function would certainly render the organ more liable to bacterial invasion and would be a factor to consider in the ultimate production of chronic cholecystitis as we see it in its final stages. Heavy precipitate and pigment concretions as seen in these hypothyroid dogs might easily be nidi about which stones might form if infection were superimposed upon the condition already present. In view of this, the hypothyroid state merits consideration as a contributing cause of cholecystitis and cholelithiasis and should be borne in mind when these patients are seen.

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PRESACRAL NEURECTOMY FOR INTRACTABLE VESICAL PAIN AND NEUROGENIC VESICAL DYSFUNCTION

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PRESACRAL neurectomy has been performed less and less frequently of late and at the present time is only rarely resorted to for the relief of intractable vesical pain and for the treatment of neurogenic vesical dysfunction. The reason or reasons for the present disinterest in this procedure may be either its apparent failure to meet the expectations originally held for it or else its gradual replacement by other procedures of proved and established merit. A review of all the cases in which presacral neurectomy has been performed at the Mayo Clinic for the relief of intractable vesical pain and neurogenic vesical dysfunction indicates that both of these factors have been responsible for the less frequent employment of this procedure. As 10 years or more have passed since the first presacral neurectomy was performed at the clinic, it seemed like an appropriate time to review and to report the results of our experience with this procedure. Furthermore, it would seem desirable to reexamine the rationale of this procedure, particularly in view of the recent changes that have occurred in our concept of the theory of micturition and in our comprehension of the respective roles played in it by the sympathetic and parasympathetic divisions of the autonomic nervous system.

HISTORICAL REVIEW

The French school of neuroanatomists and neurosurgeons is responsible for the original investigative work and for much of our present knowledge of the rôle of the sympathetic nervous system in the innervation of the pelvic viscera.

Jaboulay in 1898 first suggested paralyzing the sacral sympathetic nerves for the relief of certain types of pelvic neuralgia. For this purpose, he advocated a retrorectal approach and advised resecting the coccyx and retracting the rectum forward until the sacral sympathetic chains and the sacral ganglia were exposed. Section of these nerves usually resulted in some relief of vesical pain and in a temporary retention of urine. Later, others tried to obtain similar results by the injection of air or of artificial serum into the pelvic tissues but, as the results were unsatisfactory, the method soon was discarded.

Rochet and Latarjet in 1913 suggested the transperitoneal route for section of the nerves to the lower end of the ureter and to the bladder or the extirpation of the hypogastric ganglion. He employed this procedure for the relief of pain in tuberculous cystitis. However, since he claimed that permanent urinary retention usually followed the operation, it was gradually abandoned.

Leriche, Hallopean, Jianu, and Cotte developed hypogastric periarterial sympathectomy. Cotte in 1925 reported his first cases in which presacral neurectomy (Cotte's operation) was performed and listed the indications for the operation as follows: (1) pelvic neuralgia, (2) vaginismus, (3) rebellious dysmenorrhea, (4) uterine hypoplasia with scanty menstruation, (5) metrorrhagia and leucorrhea of ovarian origin, and (6) sexual hyperexcitability, masturbation, and so forth. Cotte later suggested its use for the relief of intractable vesical pain. Pieri (1926) also performed presacral neurectomy for the relief of vesical pain but subsequently modified the operation to include resection of the lateral sacral and lower lumbar sympathetic ganglia.

All the aforementioned investigators performed the operation primarily for the relief of pain, and it was not until Richer in 1929 treated atony of the bladder and of the colon by presacral neurectomy that this operation

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was used for the treatment of neurogenic vesical dysfunction. Learmonth (18) in the same year also performed presacral neurectomy for this same purpose, in addition to employing it in cases of severe vesical pain. The results of his work (21) and that of his co-workers form the basis of this report.

THEORY OF MICTURITION

At the time presacral neurectomy was eliciting the most widespread interest, the prevailing theory of micturition was that expressed by Jackson, who in 1916 suggested that (1) the sympathetic (thoracicolumbar) outflow controlled the mechanism of vesical filling by bringing about a state of contraction or increased tone of the sphincteric region and an inhibition or condition of decreased tonicity of the detrusor region, and that (2) the parasympathetic (sacral) outflow controlled the mechanism of vesical emptying by causing an increased degree of tone of the detrusor muscle and an inhibition of the vesical sphincter. This idea was not original with Jackson but merely represented a summary of the current impressions prevalent at the time, and for which the researches of Stewart, Elliott, and Barrington (1, 2) were particularly responsible. Furthermore, the sympathetic nervous system also was considered to be a relatively important pathway for the transmission of sensation from the bladder, particularly the sensation of vesical distention.

During the past 10 years the conception of a dual innervation of the urinary bladder as advocated by Jackson has undergone certain fundamental changes, particularly as a result of the work of Denny-Brown and Robertson (5, 6) and that of Langworthy and his coworkers (16, 17). At the present time it is rather generally agreed upon by many workers in this field that the parasympathetic innervation of the bladder is the more important one and that the sympathetic innervation is of relatively little importance. Furthermore, it also is conceded that severe vesical dysfunction results only when there is interference with the parasympathetic innervation (sacral or micturition reflex) and that few changes occur as a result of damage to the sympathetic pathways; in fact, the sympathetic innervation of the urinary bladder can be largely dispensed with without causing any significant interference with normal micturition. According to Nesbit and McLellan, the exact function of the sympathetic outflow is still open to debate, although they said that most observers "agree that impulses carried by these pathways regulate the tone of the so called internal sphincter, the trigone of the bladder, and the ureterovesical orifices. They also regulate contraction of the prostate, seminal vesicles, and ejaculatory ducts." It is also rather well established that vasoconstrictor fibers are carried in the sympathetic nerves. Most investigators today are more or less in agreement with Nesbit's views regarding the function of the sympathetic pathways, but some do not agree with the idea that the sympathetic innervation regulates the tone of the internal sphincter. In fact, many men have questioned the existence of an internal vesical sphincter. Among these men are Van Duzen who said, "after dissecting many human bladders, both male and female, I have found no suggestion of a separate muscular structure which writers in the past have chosen to call the internal urethral sphincter." He did, however, find fibers which encircled this area and by their position were capable of exerting sphincteric action, but these fibers were a continuation of the detrusor fibers and had the same nerve supply as the detrusor muscle. It was his impression that the only separate muscle of the bladder was the trigonal muscle and that it was innervated by the hypogastric or sympathetic nerve. According to Dragonas, the dilator of the neck of the bladder is the external longitudinal layer of the detrusor muscle, particularly the posterior longitudinal band. Langworthy, Kolb, and Lewis (17) expressed the opinion that the internal sphincter is merely the point of interlacement of the circular and longitudinal muscles at the neck of the bladder and that there is no true muscular development at this point. Griffiths, in 1895, also denied the existence of a true internal sphincter. Thus, some evidence indicates that a sphincter or sphincter-like mechanism at the vesical neck may be related to the detrusor muscle and as such would be innervated largely by the parasympathetic system.

Many investigators have endeavored to relax the neck of the bladder and to alter the so called urethral resistance by sectioning the hypogastric nerves. Among these were McCrea and Macdonald (1934), who concluded that section of these nerves did not cause relaxation of the internal sphincter of the bladder either in the cat (Barrington) or in man. Furthermore, they were unable to obtain experimentally any evidence of a convincing nature of either an inhibitor or excitor action on the sphincter. Denny-Brown and Robertson also denied the existence of any such effect. Van Duzen (1937) concluded from his researches on the rhesus monkey that section of the presacral nerve did not result in any relaxation of the internal sphincter and that stimulation of the nerve resulted only in a contraction of the trigone. It was not followed by either contraction of the internal sphincter or relaxation of the detrusor muscle. Langworthy, Drew, and Vest (16) in 1940, found that the urethral resistance of the cat was not appreciably affected by section of the abdominal sympathetic trunks and concluded that "abnormalities of micturition due to injury of the nervous system are dependent primarily on difficulties of contraction of the detrusor muscle and only secondarily to changes in urethral resistance. The term 'sphincter disturbance' is a misnomer."

All of the previous discussion has dealt with the possible rôle of the sympathetic system in the regulation of the tone of the internal sphincter or in the control of the so called urethral resistance. Little or no mention has been made of the sympathetic system as a pathway for the transmission of sensory stimuli from the bladder. Since presacral neurectomy originally was designed to relieve pain by the direct interruption of the principal sensory pathways, it is not surprising that the results have been disappointing, since relatively few of the sensory impulses are carried by the hypogastric nerves. Quinby (1931), in reporting a case in which interstitial cystitis was treated by presacral neurectomy, remarked: "When one considers that the urinary bladder may send afferent impulses through three different nervous pathways, it would seem doubtful that the removal of only one, and that a rather minor one, could bring sufficient relief to be of significance." Learmonth (20) was of the same opinion and in 1931 said: "I do not feel that vesical pain can be completely controlled by section of the presacral nerve." That some relief of vesical pain occurs after presacral neurectomy is apparently true, particularly relief from the feeling of intolerable distention before micturition. Learmonth (20) in 1931, Foulds (1932), McConnell (1933), and Douglass (1934) reported evidence to support this point of view. According to Cheetham (1937), this relief of pain "has been attributed to relaxation of the internal sphincter with relief of spasticity, to the cutting of some sensory fibers in the hypogastric nerve, and to the vasodilatation which may relieve pain occurring as the result of ischemia of the bladder wall." Furthermore, the relief of pain, when it was obtained, usually was only partial. Nesbit also has reported relief of pain and vesical spasm by presacral neurectomy in cases of intractable infection of the bladder. He said that the operation should be performed only in those cases in which pain is clearly demonstrated to result from spasm of the vesical outlet.

Learmonth (19) was well aware that many problems still remained unsolved. In fact, his article was prefaced by the following statement: "The surgeon must be on his guard against over simplification of any problem in pelvic surgery in which interruption of the sympathetic nerves to the pelvis seems at first sight to be logical." McCrea and Macdonald in 1934, in considering the rationale of the procedure, remarked: "It may be said without fear of contradiction that in spite of the attentions of many brilliant workers, the functions of the autonomic nervous system are even now only beginning to be understood, and it is certain that our knowledge of the nervous control of the bladder is far from complete." It was their impression that although presacral sympathectomy may have a place in the operations on the bladder, it would suffer discredit if too much is expected from it. Learmonth (19) also realized that in treating neurogenic vesical dysfunction by presacral sympathectomy he could not hope to restore normal vesical function but thought

TABLE I.—VESICAL PAIN: CLINICAL DIAGNOSIS AND RESULTS OF PRESACRAL NEURECTOMY IN 37 CASES

Diagnosis		Cases	Relief of pain		
			Complete	Partial	None
Interstitial cystitis	Typical, including chronic cystitis	17	1	4	12
	Atypical	16	2	5	9
Vesical tumor		3		1	2
Tuberculous cystitis		1			1
Total		37	3	10	24

that it might be well worth while to substitute one abnormal function for another, provided the substituted function, although abnormal, was wholly satisfactory in the economy of the patient. Furthermore, Learmonth (19) also raised the question of whether one could alter the economy of any viscus, possessing a considerable degree of autonomy in itself, merely by the division of its extrinsic innervation. However, despite the several apparent shortcomings of this procedure, he advocated its use in acquired lesions of the sacral segment of the spinal cord, or of the pelvic nerves, provided the patient was continent and the musculature of the bladder was not completely paralyzed. He also advocated its trial in instances of intractable vesical pain, although he remarked that complete relief was obtained only when the pelvic plexus itself was removed. This, of course, resulted in permanent urinary retention and necessitated the use of a catheter for the remainder of the patient's life. Thus it is evident that presacral neurectomy was far from being an ideal surgical procedure, although it offered sufficient encouragement to warrant its trial in selected cases.

POSTOPERATIVE RESULTS

A review of the surgical records of the Mayo Clinic disclosed that presacral neurectomy has been performed in 37 cases of intractable vesical pain and in 25 cases of neurogenic vesical dysfunction. In these two groups of cases, the patients were distributed about equally according to sex.

Vesical pain. The clinical diagnosis and the results of presacral neurectomy in the 37 cases of intractable vesical pain are shown in Table I. It is apparent that the operation produced a variable degree of relief of pain in approximately a third of the cases. In most of these cases the relief was only of a partial or temporary nature. It usually lasted several months to a year. In several cases the degree of pain was lessened permanently. In 3 cases there was complete relief of pain. In most of the cases of interstitial cystitis in which there was reduction of pain, the degree of the urinary frequency was only slightly improved. Little or no difference was noted in the degree of improvement in those cases in which only a simple presacral neurectomy was performed and in those in which the lumbar sympathetic ganglia also were excised.

In 5 of the cases subsequent operation was performed for relief of pain. The following operations were performed: injection of alcohol into the sacral nerves in 2 cases, suprapubic cystostomy in 2 cases, segmental excision of the bladder in 2 cases, ureterostomy (cutaneous) in 1 case and ureterosigmoidostomy in 1 case.

The treatment of painful cystitis which has been found in recent years to give most relief consists of daily instillations of solutions of silver nitrate in increasing concentration and overdistention of the bladder while the patient is under anesthesia. In 3 of these cases of intractable pain, despite these measures, cystectomy with bilateral transplantation of the ureters into the sigmoid colon was employed.

Neurogenic vesical dysfunction. In the 25 cases of neurogenic vesical dysfunction, presacral neurectomy was performed in an effort to enhance the ability of the patients to micturate. Some measure of permanent relief was obtained in only 6 cases. The relief in these 6 cases, however, was not entirely satisfactory and in 5 cases it proved to be only partial.

It is apparent that presacral neurectomy has not been of permanent benefit in most of our cases of neurogenic vesical dysfunction. However, the fact that complete relief occurred in 1 case and partial relief in 5 other cases should indicate that section of the sympathetic fibers must have some influence on

the muscles of the vesical neck. Pathologic changes in the tissues of the vesical neck were so extensive in most of these cases that dysectasia and obstruction resulted, which necessitated local measures. Transurethral prostatic or vesical neck resection was performed in 9 cases with complete relief of symptoms.

The 25 cases have been classified as cases of neurogenic vesical dysfunction since they represent a group of cases in which the patients were unable to micturate satisfactorily or to empty their bladders completely and in which cystoscopic examination failed to reveal any definite evidence of obstruction of the vesical neck. Preoperatively, a wide variety of diagnoses, including neurogenic bladder, cord bladder, atony of the bladder, paralysis of the bladder, vesical paresis, myelodysplasia with neurogenic bladder, and neuromuscular imbalance of the bladder, were made. The wide variety of diagnoses is indication in itself of the unsettled state of understanding that existed and perhaps still exists regarding neurogenic vesical dysfunction. In view of the fact that it now is realized that pathologic changes in the tissues of the vesical sphincter are the cause of retention in most atonic bladders, it is very evident that these cases of so called neurogenic vesical dysfunction included many cases of unrecognized obstruction of the vesical neck. In most of these cases, retention of urine is now relieved by transurethral resection of the sphincteric tissue. This possibility was suggested by Learmonth and Braasch (23).

The effect of presacral neurectomy on sexual function is somewhat variable, although the power of ejaculation usually is lost. Erections usually are unimpaired and orgasm occurs normally. Nocturnal orgasm occurs as before operation but emission usually is absent or greatly diminished. Sexual libido and satisfaction are ordinarily unimpaired, although some decrease in libido and satisfaction may occur. Male patients may be sterile as a consequence of the loss of ejaculation, and they should be informed before operation of this fact. Menstruation occurs normally following operation and dysmenorrhea, when present before operation, usually disappears following operation.

POSTOPERATIVE CYSTOSCOPIC DATA

The cystoscopic findings soon after presacral neurectomy were of considerable interest. Alteration in the appearance and reaction observed in the bladder in many cases were corroboratory of the physiologic results which Learmonth and Braasch (22) suggested might follow presacral neurectomy. Among the changes noted were relaxation of the trigone, relaxation of the musculature of the vesical neck, diminution in sensation, engorgement of the blood vessels and, in an occasional case, dilatation of the ureteral orifices.

Relaxation of the muscles at the bladder neck following neurectomy, when present, was often associated with a variable degree of relaxation of the trigone. In several cases, definite sagging of the base of the bladder, posterior to the trigone, was observed. Relaxation of the trigone and vesical neck had largely disappeared in most cases when the bladder was re-examined several months later. In no case was coincident relaxation of the posterior urethra in the male observed, as often occurs in cases of locomotor ataxia.

Postoperative decrease of sensation in the bladder seemed to be present in many cases but this was often difficult to evaluate. It was estimated largely by the measure of tolerance on postoperative cystoscopy and by evidence of increase in the capacity of the bladder. In several cases, the capacity of the bladder was definitely increased. There was no diminution in sensation in the posterior portion of the male urethra. Engorgement of the smaller blood vessels in the mucosa of the bladder was noted in several cases. In several cases in which postoperative excretory urograms were made, no change was noted in the caliber of the ureters.

SUMMARY

This paper is based on a review of 62 cases in which presacral neurectomy was performed at the clinic for the relief of intractable vesical pain and for the treatment of neurogenic vesical dysfunction. Although partial or temporary relief of vesical pain often is observed, permanent relief followed only occasionally, and in this respect the operation has been

found wanting. Although permanent relief resulted in 1 case and temporary improvement in vesical function for as long as a year or more has been noted in several cases, permanent improvement usually was not observed as a result of presacral neurectomy in cases of neurogenic vesical dysfunction. Another factor responsible for the gradual disinterest in presacral neurectomy, at least when performed for vesical dysfunction, is the fact that other operative procedures, such as transurethral resection of the tissues at the vesical neck, have proved to be of greater effectiveness in providing the desired relief. The changes in the bladder noted in many cases on cystoscopic examination soon after presacral resection would offer corroboration of relaxation of the muscular tissues in the trigone and vesical neck following presacral neurectomy. These findings, together with the postoperative relief of symptoms frequently observed, although temporary, would indicate that the physiologic premises on which the operation was advocated by Learmonth and Braasch (22) were in a measure sustained.

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SOME COMPLICATIONS IN THE SURGICAL HANDLING OF CARCINOMA OF THE LEFT COLON AND RECTUM

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THE operative horizon for patients with carcinoma of the large bowel has broadened tremendously within the last decade. Procedures which were quite hazardous only a few years ago are now available with relative safety, and improvements in anesthesia, preoperative and postoperative care, surgical nutrition and rehabilitation, avoidance of peritonitis, etc., have put radical resection within the reach of many otherwise hopeless individuals. Large groups of cases are now being reported regularly with a low mortality. However, this field will always be a difficult and complicated one for any curative procedure, and one in which any operation is liable to many different complications. It is with this thought in mind that certain complications and problems which arose in the following 4 cases are discussed.

CASE 1. Mrs. Ida. K., aged 52 years, was first seen in February, 1941. Carcinoma sigmoid. Rankin obstructive resection. Necrosis of distal colostomy loop above the peritoneum. Subsequent refashioning of double barrel colostomy and later division of the spur with satisfactory closure.

Patient had been constipated for years. This condition had become worse during the past 2 or 3 months, and there had been lower abdominal cramps. The cramps had become worse during the past 10 days, but they were relieved with bowel movements. X-ray films showed an annular constriction in the midsigmoid. At operation there was an annular constricting growth in the upper midportion of the sigmoid, about 1 inch in diameter. Abdominal exploration was otherwise negative. A wide mobilization of the sigmoid was done, and the lesion, including a wide V-shaped apron of mesentery, was removed by Rankin obstructive resection. The apex of the resected mesentery was down close to the aorta. The two bowel loops were tacked together, the peritoneum closed, and the bowel amputated above the skin of the abdomen.

That evening it was noticed that the lower loop of the colostomy was dark colored. There was immediate concern for the viability of this loop. A small narrow proctoscope with a light was introduced into the lower loop. The peritoneum could be seen 2 inches below the skin surface. "Underneath this, the color of the bowel lumen seems better." Nothing was done. Four days later the end of this distal loop became gangrenous and soon sloughed off. There was no sign of any intraperitoneal complication, and the upper loop of the colostomy functioned well. Convalescence was otherwise uneventful. When she left the hospital on the 20th day after operation she had, to all intents, a well functioning single barrel colostomy. The lower segment was not visible.

Two months later the patient re-entered the hospital. The lower portion of the wound below the single-barrel colostomy was opened and the abdomen entered here. A large tongue of omentum was mobilized and freed. Then a very healthy looking lower segment of sigmoid was apparent. It began at the level of the peritoneum where the distal 2 inches had previously sloughed off and there was about 3 inches of distal colon from here to the rectosigmoid junction. This lower segment was mobilized carefully down to the pelvic floor and the two loops of bowel could then be tacked together again as a double barrelled colostomy. A spur crushing clamp was applied and the abdomen was closed. The clamp came off in due time. The patient went home on the 10th day after operation.

Two months later the colostomy was closed by simply freeing it in the subcutaneous fat, inverting the dome of bowel, and closing the skin. The patient has been well since (now 2 years).

Vascular necrosis of 1 to 2 centimeters of the distal colostomy will not produce fatal peritonitis (8), for the peritoneum seals off and supports the deeper portion of the limb of bowel. Should the bowel below the peritoneum become necrotic, lethal peritonitis may ensue. In this event, immediate laparotomy may be indicated. Hence it is important to inspect all colostomy loops within the first 12 to 24 hours after operation.

Another infrequent but very fatal complication of colon resections has been noted by Garlock. The loops having been brought out onto the skin, there is subsequent retraction of the exteriorized loop into the abdomen with resulting peritonitis. This condition is due to insufficient mobilization of the bowel,

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and not to an error in judgment of the blood supply.

With the present day preliminary bowel preparation and lessened danger of peritonitis, the major concern in bowel resections is for the adequacy of the blood supply. Certain studies indicate that dividing the bowel 2½ to 3 inches away from the growth on either side is ample; lymphatic spread along the bowel surface or lumen does not usually go beyond this distance. It is highly essential to remove a very wide apron of mesentery, however. Then it is very easy, with a long narrow tongue of mesentery resected, to omit the careful inspection of the bowel ends for blood supply.

CASE 2. Mr. Morris M., aged 68 years, was first seen in April, 1943. Large carcinoma of the lower sigmoid with obstruction. Fistula to the bladder. Devine colostomy, then Rankin obstructive resection of the lower sigmoid including a large portion of the dome of the bladder.

There had been some suspicious trouble in the sigmoid in 1936, and an x-ray diagnosis of probable polyps of the colon was made at that time and operation advised. He, however, sought other advice and refused operation. Apparently, from his description he had felt well until recently. For the past 5 to 6 months he had not felt well and said he had lost 50 pounds in weight. There had been mild abdominal pain, with some diarrhea and occasional obstructive symptoms.

For the past 2 weeks he had noticed fecal material coming from his bladder on urination. Examination showed a very pale and sallow looking thin man. A large mass could be felt in the lower left abdomen. On urination, there was a rather thick stream of fecal material with some odor. The abdomen was distended and there was complete obstruction. X-ray examination showed complete obstruction, no barium going through the sigmoid. It further demonstrated gas in the bladder indicating the location of the fistula.

On April 23, 1943, a Devine colostomy was made in the right upper abdomen. The transverse colon was enormously distended with gas and had to be aspirated. A large mass was felt in the left lower quadrant of the abdomen. A very rapid exploration revealed no further extension of the disease, except one suspicious lump high up on the dome of the liver. The transverse colon was mobilized with some difficulty because of distention, and the two loops were brought out in the right upper quadrant and divided for the Devine colostomy. The obstruction relieved in about a week and patient was sent home on May 8, 1943, for rehabilitation. During this time the distal loop of colon was thoroughly irrigated and completely "defunctionated."

On June 5, 1943, the left lower abdomen was explored. A large mass presented in the lower sigmoid region which was adherent to the parietal peritoneum. When this was carefully freed, it was found that the bladder was densely adherent to the mass and the finger could be introduced between the bladder and the sigmoid itself. The left side of the dome of the bladder was resected, an area about the size of a dollar being left attached to the sigmoid growth. There was a hard walled perforation in the center of this which communicated with the bowel lumen. The bladder was then inverted with two layers. The growth was then mobilized easily by dividing the lateral leaf of the peritoneum along the lateral sigmoid wall. The sigmoid was fairly redundant and there was fully 5 inches between the lower end of the growth and the rectosigmoid peritoneal reflection. Wide Rankin obstructive resection was done with wide removal of the apron of mesentery (Fig. 1). The spur crushing clamp was applied 3 weeks later. The sigmoid colostomy was closed July 4, 1943. The Devine colostomy was closed August 30, 1943. Patient then moved his bowels normally and on October 1, 1943, was well, although there was still some purulent discharge on urination. He was gaining weight.

Adherence of carcinoma of the sigmoid to the pelvic structures, uterus, bladder, loop of small intestines, is not a contraindication to radical removal. It is the opinion of most surgeons that these cases are not curable in any large number, but the palliation is distinctly worth while and often lasts for 1 or 2 years. It is not usual to be able to resect the bladder successfully with a growth in the sigmoid. In C. W. Mayo's report of 176 resections for carcinoma of the left colon (in which 2 out of 5 were palliative or probably palliative), there was only 1 case in which an attached bladder was resected with the growth, although there were several cases in which the bowel had been adherent and adhesions divided.

This is one situation in which the Devine colostomy was valuable. The complete "defunctioning" of the bowel allows one to resect widely, including other viscera, with more complete freedom from the fear of peritonitis than we have had heretofore.

CASE 3. Mr. M. G., aged 55 years, was first seen in February, 1943. Carcinoma rectosigmoid. Anterior resection with re-establishment of bowel continuity. Stricture at anastomotic site, released by laparotomy and freeing of omental adhesions. Second carcinoma then discovered in splenic flexure. Rankin obstructive resection.

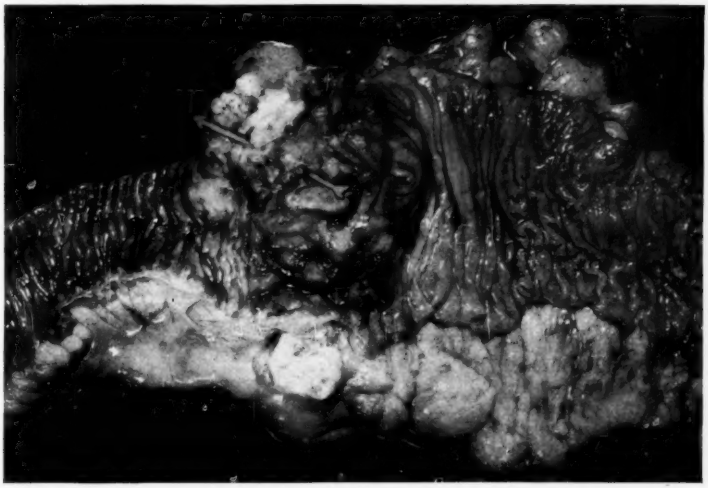

Fig. 1. Case 2. Large fungation carcinoma of lower sigmoid which has extended to and perforated into the bladder. Removed with wide excision of dome of bladder.

Patient had lost 25 pounds in the past 6 to 8 months. For the past 3 to 4 months there was heartburn, fullness after fried or spicy foods. He did not feel like eating and "felt bad" without being able to find out exactly what he meant. He had always had regular bowel movements without a laxative, but during the past 2 months his bowels moved only every other day. For the past weeks there was some lower pelvic pain.

Examination showed a fair sized individual with some evident weight loss. X-ray examination (Fig. 2) showed a constricting lesion just above the rectosigmoid junction. The descending colon and the transverse colon filled very well.

Operation on February 13, 1943, consisted of a left lower midrectus exploratory incision. An annular growth about 1½ inches in diameter, with some local involvement of the mesentery but no wide extension, was revealed. Its lower end was about 1 inch above the rectosigmoid peritoneal reflection. It was decided to do an anterior resection, after first defunctionating the colon with a Devine colostomy. The wound was closed, another incision was made in the upper right quadrant, and the proximal transverse colon was brought into the wound. A spur was formed, the two bowel ends brought out onto the abdomen through two small separate incisions 1 inch from the main incision, the wound was closed, and the bowel divided.

The colon was then thoroughly defunctionated by daily irrigations of the distal segment plus sulfasuxidine per catheter.

Second operation was performed March 9, 1943. The previous wound in the left midrectus was reopened. The sigmoid colon was very clean. It seemed to be much smaller than normal and the muscular tone was much better. The growth was about 1 inch above the rectosigmoid peritoneal reflection, which lay rather deep in the pelvis. The colon was freed in type fashion by incising the peritoneum lateralward then around the bladder and up the mesial leaf. The distal colon and rectum down to the coccyx were then freed from their attachments. When this was done there was 3 inches of bowel below the tumor and the blood supply seemed satisfactory. The superior hemorrhoidal vessels were then divided, and the growth in the colon was removed with a margin of about 2½ inches on either side of the growth, great care being taken to preserve the arterial supply of the remaining bowel ends. An end-to-end free style open anastomosis was then made between the lower stump of the rectum and the proximal end of the colon. The anastomosis was performed rather easily with very little spilling. Five grams of sulfanilamide were dropped into the wound. Abdomen was closed with a Penrose drain toward the anastomotic area. Convalescence from this operation was uneventful.

At subsequent office visits, by passing a proctoscope one could see the site of the anastomosis about 4 inches above the rectum. The proctoscope would not pass this point, however, and with some manipulation only a small amount of gas and a slight bit of fecal material could be seen coming through a pinhead sized lumen. A barium enema given March 24, 1943 and again April 17, 1943 showed complete obstruction at the site of anastomosis. No barium passed through (Fig. 3). It was decided to explore the abdomen again before an attempt was made to close the colostomy in the right upper quadrant.

Fig. 2. Case 3. Carcinoma of rectosigmoid. Preoperative roentgenogram after the administration of a barium enema, February 8, 1943.

Fig. 3. Case 3. Stricture following anterior resection and end-to-end anastomosis March 24, 1943. Released by laparotomy and liberation of omental adhesions.

On May 15, 1943, the old left rectus incision was reopened. There was some omentum adherent to the parietal peritoneum but after this was released the abdomen was relatively clean. The sigmoid colon was freed down to the pelvic brim. It was rather densely adherent, but after some adhesions were freed the colon could be seen as a well functioning tube. A rectal tube was then passed up from the anus by an assistant. It could be felt to go through the anastomotic site very easily and was palpable distinctly 2 inches above the pelvic brim inside the sigmoid colon. The wound was then closed.

It was now thought that the patient's troubles were over and the colostomy might be closed. A barium enema given June 8, 1943 revealed that the "distal part of the colon appeared to be of good caliber. The previous constriction seen in the rectosigmoid area apparently has been well dilated. The descending section of the large bowel is well shown and appears to be normal in character." However, "as the barium entered the splenic flexure a very definite point of obstruction was encountered, and only a small portion of barium could be made to pass the splenic flexure into the transverse colon (Fig. 4). This constriction was also seen by injecting barium through the distal end of the Devine colostomy in the right upper quadrant." X-ray diagnosis was neoplasm of the proximal loop of the splenic flexure. When the original film made before the first operation (Fig. 2), was reviewed it was seen that the distal portion of the transverse colon, as it ascended to the splenic flexure, was obscured by the descending limb of the splenic flexure and the portion of the colon which now showed that the constriction could not be seen clearly on the first film. After some deliberation it was decided that since the patient's general condition seemed satisfactory it was necessary to remove the second carcinoma at the splenic flexure.

On June 14, 1943, the previous incision in the left midrectus was reopened and extended upward. There was a loop of small bowel adherent to the midportion of the abdominal wall which was freed. The splenic flexure was mobilized by incising the lateral peritoneum. There was a large dense stony hard tumor which was annular and involved about 1½ inches of the bowel, just proximal to the splenic flexure. There were some small glands in the mesentery but these were soft. The splenic flexure was mobilized, the greater omentum separated off, the mesentery divided, and then a rapid Rankin obstructive resection done. A 2 inch spur was fashioned. The lymph node was normal in microscopic examination.

Fig. 4. Case 3. Barium enema given June 8, 1943, to be certain that the site of stricture in rectosigmoid was satisfactory. Barium passed here without delay. An unsuspected carcinoma discovered in splenic flexure. Compare with Figure 2 taken 4 months before.

Patient left the hospital in 2 weeks. Spur crushing clamp was applied on July 16, 1943, and again on July 30, 1943. The edema subsided, and on August 13, 1943, the spur depth was fully 1½ inches and the walls of the bowel seemed smooth. He re-entered the hospital shortly and on August 26, 1943, the left upper colostomy wound was closed, and at the same time the two loops of the Devine colostomy were closed. Convalescence was uneventful. He left the hospital 4 days after the colostomy was closed. Bowels have moved normally per rectum ever since. When last seen September 28, 1943 he was gaining weight, looked well, and felt good. There was no abdominal diastasis or weakness of either of the wounds. The long wound in the left rectus muscle, through which the abdomen had been entered five times, and which now extended from the costal origin to the pubic spine, was well healed (Fig. 5). There was no induration anywhere and no weakness or bulging whatever. Stainless steel sutures had been used.

Emphasis has been placed upon the upward spread of cancer of the rectum by several

Fig. 5. Case 3. Showing abdominal healing after 5 laparotomies. Stainless steel wire used.

anatomical studies since 1930 (2, 6, 11). The evidence is that such spread is generally upward and not downward. Now that preoperative preparation, nutritional deficiencies, protein balance, avoidance of peritonitis and pneumonia are charted and standardized procedures, anterior resection of growths at or just above the rectosigmoid has become popular (3, 4). Growths a short distance above the rectosigmoid are the most suitable for anterior abdominal resection with preservation of the sphincters, and here the Devine defunctioning colostomy finds its chief indication. However, some do an anterior operation for growths lower down (10), for tumors within 10 to 13 centimeters of the anal opening.

Time has not yet elapsed for final statistical evaluation. We have seen a few perineal extensions of far advanced carcinoma of the rectosigmoid. Jones states that a lesion whose lower edge is at the peritoneal reflection of the rectosigmoid or 2 inches above it should have the same operation as those listed under carcinoma of the rectum; for him, that is abdominoperineal removal with a permanent colostomy. He is not satisfied that any lesser

Fig. 6. Case 4. Abdominoperineal resection. Post-operative care. Photograph taken on 6th day after third operation. *A*, Colostomy opening; *B*, enterostomy tube; *C*, urinary catheter with irrigation; *D*, continuous intravenous glucose and saline, etc.; *E*, Miller-Abbott tube with suction (lower small bowel); *F*, Levine tube with suction (stomach); *G*, aspirator for nasal and pharyngeal secretions; *H*, oxygen tent.

procedure with preservation of the anus will show as high a cure rate.

Stricture blocking the anastomotic site is not unknown. Fallis mentions it as having occurred in 3 of 31 cases. One of these required permanent colostomy, the other 2 were kept patent by repeated dilatations. Allen states that "stricture, requiring tedious dilation, results if the anastomosis is placed below the pelvic floor."

In the case described the stricture was above the pelvic floor and was due to omentum wrapping itself about the anastomosis and apparently was not due to narrowed mucosal lining *per se*.

Some men advocate an aseptic end-to-end anastomosis. This is rather difficult to do deep down in the pelvis. In our experience with this case, the free type anastomosis with the open ends of bowel was quite satisfactory and there was no infection or contamination.[1] The reasons for this probably were the absolute emptiness of the bowel plus the partial sterilization of the contents with sulfasuxidine. Sulfasuxidine, as several have noticed and we have also observed, will decrease the Bacillus coli content of the stool from 10 million per cubic centimeter to 10 thousand per cubic centimeter.

Two new-growths in the colon occurring either simultaneously or within a few months of each other are not unusual. It is unusual, however, suddenly to find the second growth at the splenic flexure, after the first one at the rectosigmoid has been finally removed. Whether this was a new development which started in the 6 month interval between the first operation and the removal of the splenic flexure growth, or was small and obscured at the first x-ray examination by the descending limb of the splenic flexure, we cannot say. This finding simply re-emphasizes the care and attention to detail which management of these cases must have in every phase of treatment.

CASE 4. Mr. Sam B., aged 54 years, was first seen in August, 1943. Abdominoperineal resection. Mechanical intestinal obstruction. Two postoperative explorations for relief of obstruction. Recovery.

[1]Fallis, who uses aseptic anastomosis in anterior resection, states "an open anastomosis is just as readily carried out and perhaps permits more accurate suturing."

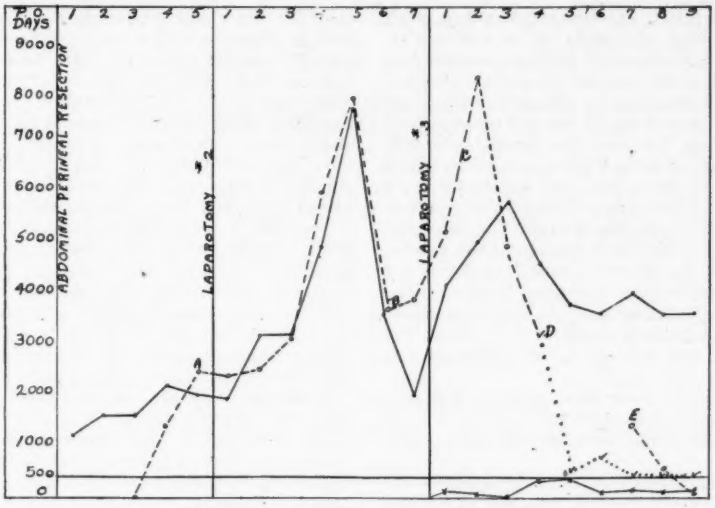

Chart 1. Case 4. Abdominoperineal resection. Intake and output from gastrointestinal canal. *A*, Levine tube output greater than oral intake, first obstruction. *B*, Same reversal. Second obstruction. *C*, Continued reversal after third laparotomy, meanwhile drainage from enterostomy tube started. *D*, Miller-Abbott tube suddenly passed pylorus, 90 hours after it had been placed in front of pylorus by fluoroscopic control. Oral intake has been greater than output for 24 hours. *E*, Gastric distention developed while Miller-Abbott tube was in lower small bowel, second Levine tube reinserted. •—•—•, Oral intake; o—o—o, Levine tube output; . . . ., Miller-Abbott tube output; x—x—x, enterostomy tube output.

Patient had been well until 3 to 4 months before, when he had noticed occasionally a slight streaking of blood in the bowel movement. For the past 6 weeks this streaking had increased, so that he had had several dark black stools, and within the last 3 weeks there had frequently been fresh blood in the stool. For the past 6 weeks there had been general malaise and loss of strength; also frequent bowel movements with a sense of incomplete evacuation. For 1 week there had been some lower abdominal cramps. There had been no weight loss, no constipation.

General examination revealed a moderate sized man in fair health, with evident anemia, but otherwise negative except for the rectal condition. Here, on the posterior surface well within reach of the examining finger was a large ulcer about the size of a dollar which had a curled hard edge and did not seem densely attached to the posterior structures. Microscopic examination revealed carcinoma.

On August 21, 1943, a combined abdominoperineal resection was done. There were no glands palpable in the mesentery of the sigmoid. A hard mass was felt high up on the superior surface of the liver underneath the dome of the diaphragm. It was about 1.5 centimeters in diameter and beneath the surface of the liver. Since abdominal exploration was otherwise negative, and such a liver nodule reached only by the palpating finger was not absolute proof of a metastatic deposit, the case was deemed suitable for abdominoperineal resection. The operation proceeded uneventfully, as was thought. When the pelvic peritoneum was closed, it was done so "very easily except at one place where there was a minimal amount of tension on the suture line." This tension was high up, close to the root of the colostomy limb. It was not thought significant at the time. Certainly we have closed the pelvic peritoneum under more tension in other cases.

The posterior resection of the rectum was done partly with the cutting coagulation current. A wide Metcalf pack surrounded by cellophane was packed into the perineal wound.

Immediate postoperative reaction was satisfactory. The perineal pack was removed in 24 hours. Temperature remained at 99 degrees for the first 4 days. However, on the 4th day, the Levine tube began putting out more than he took in by mouth (clear fluid had been given by mouth) (Chart 1, *A*).

On the 5th day it was evident that obstruction was present. There was increasing abdominal distention, the output through the Levine tube increased, and early in the evening large quantities of dark fluid, with a high intestinal odor, drained continuously from the stomach. Nothing had come through the colostomy opening. It was decided to explore the abdomen.

The second operation was performed on August 26, 1943. Under spinal anesthesia the wound was re-opened. At the site where the posterior peritoneum had been closed under tension the peritoneum had separated over an area about 1 inch in diameter, and at this point the posterior wall was not covered with peritoneum. Over this area the small bowel was stuck tight and there was a small abscess from which about 1 ounce of thick pus was evacuated with suction. The small bowel was dilated above and was narrow below the site of obstruction. The omentum would not stretch sufficiently to cover the denuded area. Because of the patient's condition it was not deemed advisable to do anything further. The bowel was rapidly released and the abdomen closed with through-and-through stainless steel wires. The perineal wound was re-opened and drainage was instituted.

Immediate reaction from this operation was precarious. The pulse remained at 160 for 2 days (Chart 2) and patient was in a semicomatose condition.

Supportive treatment consisted of: parenteral fluids, kept at about 3000 cubic centimeters 4 times a day. Urinary output ranged from 1500 to 2000 cubic centimeters. Sulfanilamide had been put into the peritoneum (12 gms.) and sulfadiazine was continued intravenously (6 gms. 4 times a day) so that a blood level of 9.3 was obtained. Nourishment was provided by 3000 cubic centimeters of 5 per cent glucose (150 grams) plus about 100 grams of protein administered added to the intravenous fluids, either as amigen (Mead Johnson) or aminoacids (Stearns) (Chart 2).

Patient was quite thirsty and he was given rather large quantities of water by mouth, since these returned immediately though the Levine tube. The 2d day after this he passed gas through the colostomy and 2 days later had one small liquid stool. It was thought our troubles were ended. However, no more gas or bowel movement came from the colostomy. On the 7th day after operation on September 2, 1943 the Levine tube again was putting out 1000 cubic centimeters more than the fluid intake by mouth (Chart 1, *B*). Temperature remained between 100 and 101 degrees, pulse 110 and 120, and the patient's condition was only fair. He was irrational, confused, and restless.

On September 2, 1943, a portable flat x-ray film showed much gas in the small bowel, although abdominal distention was not marked.

The patient was taken to the x-ray department. A Miller-Abbott tube was passed, and under frequent fluoroscopic observation it was kept in front of the pylorus for 4 hours, but it made no further progress. It was decided to risk another laparotomy because the obstruction had evidently not been relieved.

At 8:00 p.m. on September 2, 1943, the old incision was reopened. The pelvis was occupied by a large mass of distended small bowel. The rent in the posterior peritoneum had become somewhat organized but there was a granulating surface fully an inch in diameter. There was some greenish inflammatory exudate about this area and two or three loops of small bowel were adherent to it, and covered with some exudate. The remaining loops of small bowel did not have any gross inflammatory exudate about them. They were distended, however, and were stuck together by plastic adhesions which separated with difficulty, and the omentum was spread over their surface rather tightly.

The omentum was mobilized and brought down, and by dividing it into two tongues by longitudinal incision one was able to tack it over the rent in the posterior peritoneum. Because the loops of small bowel could not be separated a rapid Witzel type enterostomy was done. This was brought up through the omentum, and the wound was again closed with through-and-through wire sutures.

Immediate reaction was only fair. Patient was still only semiconscious. The enterostomy tube drained 200 cubic centimeters within the first 24 hours, then drained intermittently and 3 days later drained again another 300 cubic centimeters. For 2 days his duodenal balance was negative by rather large amounts—100 to 3000 cubic centimeters (Chart 1, *C*). The Miller-Abbott tube had been left *in situ* and functioned as a Levine tube keeping his stomach empty. After 90 hours it suddenly passed the pylorus (Chart 1, *D*), then it descended rapidly and evacuated 3000 cubic centimeters. Nutrition was still maintained solely by intravenous injection, 3000 cubic centimeters in 24 hours, which included 150 grams of glucose plus 45 grams of aminoacids. He was still in the oxygen tent and was only partially rational during this entire period.

As soon as the Miller-Abbott tube began functioning, he improved. His distention relieved and he became clearer. However, on the 6th postoperative day following the 3d operation, distention was noticed in the upper abdomen. A Levine tube was inserted through his opposite nostril into the stomach and a second suction apparatus attached (Chart 1, *E*). Now the patient had tubes in both nostrils, connected to two separate suction apparatuses on the right side of the bed, an intravenous fluid outfit going into his right arm, an enterostomy tube draining into a bottle on his left side, a permanent catheter in his bladder draining to the left side, a perineal dressing with tubes for irrigation, and an oxygen tent (Fig. 6). The Levine tube drained 1000 cubic centimeters for 2 days, then the abdominal distention relieved.[1]

On the 8th postoperative day, gas was passed through the colostomy. Troubles were not entirely over, however. A large tender mass was felt and seen in the right upper abdomen, which area had been sore for 2 or 3 days. After some consideration it was decided to aspirate this mass with a thin

[1]Wangensteen speaks of the fact that "if the Miller-Abbott tube placed well down in the reaches of the small intestine, is used as a prophylaxis against intestinal distention, often it is found necessary to put an additional tube down through the patient's other nostril into his stomach."

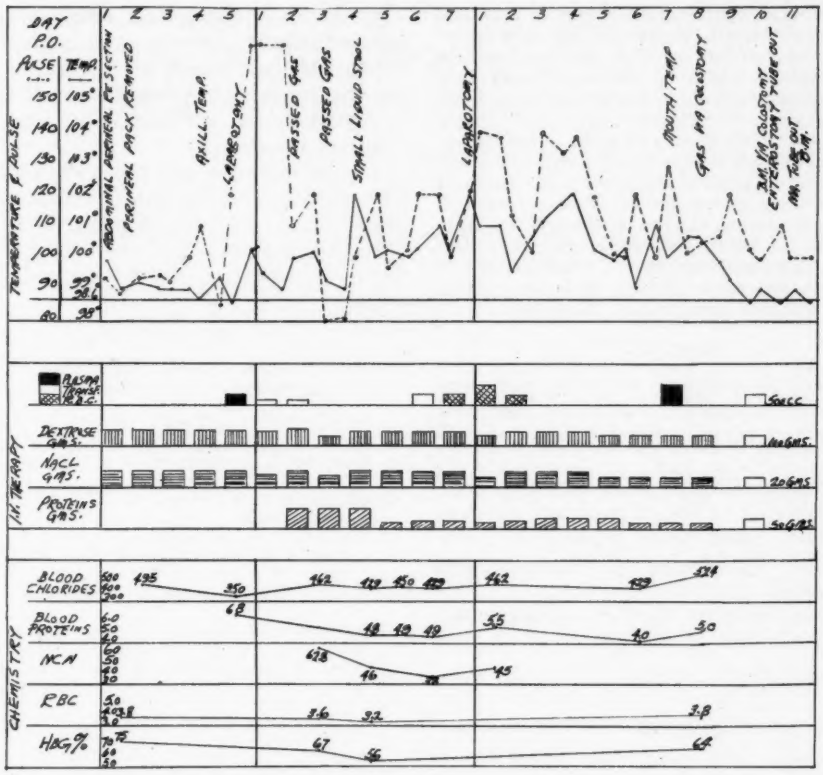

Chart 2. Case 4. Abdominoperineal resection. Temperature and pulse graph. Intravenous therapy. Blood chemistry determinations. Urinary output, 1500 to 2000 daily. Dextrose given as 5% dextrose in N.S.; proteins either as amino acids (Stearns) or amigen (Mead Johnson); cevalin 300 mgm. daily, betalin 2 c.c. daily.

needle. One hundred cubic centimeters of rather thin fluid with an odor was evacuated. It was felt that this was a distended loop of small bowel which was still somewhat caught in the inflammatory process. This relieved him, and no untoward effects were noticed from the aspiration of the bowel itself.

September 12, 1943, 11th postoperative day after 3d operation, he had a large copious bowel movement through the colostomy. Except for one small liquid stool 4 days after the 2d operation, this was the first bowel elimination the patient had had for exactly 21 days. The Levine, enterostomy, and Miller-Abbott tubes were removed on the 9th, 10th, and 11th postoperative days (after 3d operation), respectively.

The chloride balance had been fairly well maintained throughout the entire course (blood chlorides 425 to 450 mgm.). Urine output remained about stationary. However, there was difficulty in maintaining the blood protein level. On September 8, 1943 (6th postoperative day after 3d operation) the total blood proteins were 4.0. The next day 1000 cubic centimeters of plasma was given. Patient visibly improved but the following day the blood proteins had been raised only to 5.0 (Chart 2). From then on the convalescence was relatively uneventful. The colostomy functioned very well. There were occasional periods of some distress when tenderness could again be appreciated in the right upper quadrant, but there was no suggestion of any further filling of an isolated loop of small bowel. Patient was out of bed September 13, 1943. The wound healed *per primam:* sutures were removed on September 18, 1943, and there was no weakness in the abdominal wall. Colostomy worked very well with no delay for the past day or two before discharge. Patient ate everything. He was discharged from hospital September 27, 1943.

Résumé Case 4. Combined abdominoperineal operation was done. Pelvic peritoneum was inadvertent-

ly sutured with slight tension. Signs of intestinal obstruction developed 4th and 5th day after operation. Wound was reopened. A gap was found in posterior peritoneal suturing with small bowel stuck to it and localized abscess. Obstruction was relieved and abscess drained. Colostomy functioned 2 days, and then obstruction developed again. Third operation was performed 6 days later. Small bowel was found matted together in the pelvis, and the site of the rent in the posterior peritoneal closure was still open and granulating, and the small bowel was again adherent to it. Omentum was sutured down here as a large tongue and enterostomy was done. Miller-Abbott tube passed the pylorus 90 hours after its insertion, and then bowel finally functioned.

SUMMARY

Four cases of resections of the left colon and rectum are reported, illustrating different problems and complications which were encountered:

1. Necrosis of distal colostomy loop after Rankin obstructive resection of carcinoma of the sigmoid; spontaneous separation above peritoneum; refashioning of colostomy spur and successful closure.

2. Fistula between sigmoid carcinoma and bladder; resection of a segment of bladder with the tumor.

3. Anterior end-to-end resection of low sigmoid growth; stricture at anastomotic site, relieved by laparotomy and liberation of adhesions; second carcinoma discovered at splenic flexure during convalescence; Rankin obstructive resection.

4. Abdominoperineal resection; postoperative intestinal obstruction (mechanical ileus) from insecure suturing of posterior peritoneum; two postoperative abdominal explorations for release of obstruction; satisfactory recovery.

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LIGATION OF THE THORACIC DUCT AND THE POSTHEMORRHAGE PLASMA PROTEIN LEVEL

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IN a previous communication from this laboratory (4), it was reported that after hemorrhage the concentration of proteins in the thoracic duct lymph underwent a considerable increase. On the basis of this finding, it was suggested that the lymph serves an important rôle in the compensatory mechanism of hemorrhage, not only as a pathway for fluid, but also as a source of protein replacement.

The present work is an attempt to assay the rôle of the thoracic duct, the principal lymph-collecting channel, in the maintenance of the plasma protein level after acute hemorrhage.

METHOD

Twenty-five dogs, all in normal nutrition, were used in this work. They may be divided into two groups—group I, 15 animals in which hemorrhage was instituted after ligation of the thoracic duct; group II, 10 control animals in which hemorrhage was instituted with the duct intact. In 2 of these animals, an incision was made in the neck similar to that in the animals in group I, but no ligation of the duct was performed.

The animals were all weighed prior to the experiment, and a sample of blood was taken from the jugular vein for hematocrit and plasma protein determinations by the Barbour-Hamilton falling drop method, heparin being used as anticoagulant. Anesthesia was induced by injecting 1 cubic centimeter of 3 per cent pentobarbital per kilogram (intravenously). Fifteen minutes after the induction of anesthesia, another sample of blood was taken for a second set of hematocrit and plasma protein determinations. The animals in group I were then subjected to ligation of the thoracic duct close to its entrance into the left subclavian and internal jugular veins through a low collar incision in the left side of the neck. After closure of the operative wound, the animals were bled 25 per cent of the estimated blood volume without ligature of the thoracic duct.

The hematocrit and plasma protein values of both groups were again determined 1 to 4 hours after hemorrhage and twice daily thereafter for a period of 9 to 13 days. The post-hemorrhage diet of the animals in both groups, except for dogs 16 and 22, consisted of water and milk *ad libitum*, and the standard kennel diet of purina "dog chow" adequate both for proteins and calories. Dog 16, belonging to group I and dog 22 to group II were placed on a nitrogen-free diet, throughout the course of the study, in order to determine the influence of diet on the course of the plasma protein curve.

RESULTS

Effect of anesthesia. Prior to the administration of the anesthetic agent, the initial hematocrit readings ranged between 45 and 55 per cent, the specific gravity of the plasma averaged 1.0250, and the plasma protein level averaged 6.15 grams per cent. Following the induction of anesthesia, there was an average fall in the hematocrit readings of 5 volumes per cent in all the animals of both groups. The effect on the specific gravity of the plasma varied. In 11 animals, there was a slight drop; in 10, no alterations occurred; and in 5, there was a slight rise.

Effect of hemorrhage on hematocrit values. In all cases the hematocrit values continued to fall after hemorrhage, there being an average 15 per cent volume decrease within 24 hours. The hematocrit value continued to decline on subsequent postoperative days in all cases, except 1 in group I, and 2 in group II, which

With the technical assistance of Lily Schmidt and Arthur Wallen from the Laboratory of Experimental Surgery, New York University College of Medicine.

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TABLE I.—PLASMA PROTEIN PATTERN FOR GROUPS I AND II

Time	Peak of decline No. of animals—%	Incipient rise No. of animals—%	Return to normal No. of animals—%	No return No. of animals—%
A. Thoracic duct ligation followed by hemorrhage—				
24 hrs.	2—13.3	0	0	0
2 days	10—66.6	1— 6.7	0	0
3 days	1— 6.7	2—13.3	0	0
4 days	1— 6.7	5—33.3	0	0
5 days	1— 6.7	5—33.3	0	0
6 days		1— 6.7	1— 6.7	0
7 days		0	1— 6.7	0
8 days		1— 6.7	0	0
9 days			5—33.3	0
10 days			3—20.0	0
11 days			1— 6.7	0
12–14 da.				4—26.6
B. Hemorrhage without ligation of the thoracic duct—				
4 hrs.	5—50.0	0	0	0
12 hrs.	0	3—30.0	0	0
24 hrs.	4—40.0	5—50.0	3—30.0	0
2 days	1—10.0	1—10.0	3—30.0	0
3 days		1—10.0	2—20.0	0
4 days			0	0
5 days			2—20.0	0

demonstrated an average rise of four volumes per cent, about the 9th to 11th day. The average total fall of hematocrit values for all groups was 18 volumes per cent.

Effect of hemorrhage on the plasma protein level. The behavior of the plasma protein curve followed two distinct patterns, each represented by one of the groups.

In group I, it is seen from Table I, that the plasma protein concentrations continued to decline to a minima in 2 to 3 days posthemorrhage, the minima averaging 0.6 to 1.8 grams per cent. The curve then began to rise by about the 5th day in all but 2 of the animals (86.6%). Most of the animals reached normal on the 9th and 11th day (60%). Four animals (26.6%) showed no recovery of the plasma protein level even after 13 days of observation. In only 2 cases (1.3%) did the specific gravity of the plasma return to the prehemorrhage level earlier than the 9th day. Animal 18, which was on the nitrogen-free diet, followed the typical pattern of the other animals of this group.

In group II (Table I) the fall in plasma protein concentration occurred sharply within the first 48 hours with no further decline thereafter. In 3 of the 10 animals, there was a definite trend toward normal, beginning in 6 to 12 hours after hemorrhage. The rise had begun within 24 hours in 8 of the 10 cases (80%); 3 (30%) returned to normal within 24 hours, and 6 (60%) within 48 hours. In only 2 animals was there a delay of 5 days. It was also noticed that all animals of this group were definitely more active than those of group I from the 3d to 8th day after. Animal 22 in this group with the nitrogen-free diet showed the same group pattern, reaching normal within 28 hours.

In addition, there were 3 other animals originally subjected to the same operation as those in group I, but they were not included in Table I because 2 had postoperative infection, and 1 had died 5 days after operation from secondary hemorrhage caused by a slipped ligature of the femoral artery. The first 2 animals were killed during the 2d week, at which time autopsy showed dilation and enlargement of the lymphatics of the thorax and abdomen, but no chylothorax or chyloperitoneum. The cisterna chyli was intact in both. Autopsy of the 3d dog, 5 days after operation, revealed similar findings.

Additional experiments. Three animals from group I, 12 weeks after the thoracic duct ligation and first hemorrhage were subjected to a second hemorrhage. The plasma protein pattern this time resembled that of the animals of group II. Their results are included in group II.

Figure 1 is a chart showing two sets of curves: (a) hematocrit and plasma protein levels after thoracic duct ligation and hemorrhage, and (b) that following hemorrhage in one of the dogs of group II. Figure 2 is a chart of the same dog of group I, showing curve of second hemorrhage 12 weeks later.

OBSERVATIONS

The striking difference in the pattern of the return of the plasma protein curves in the

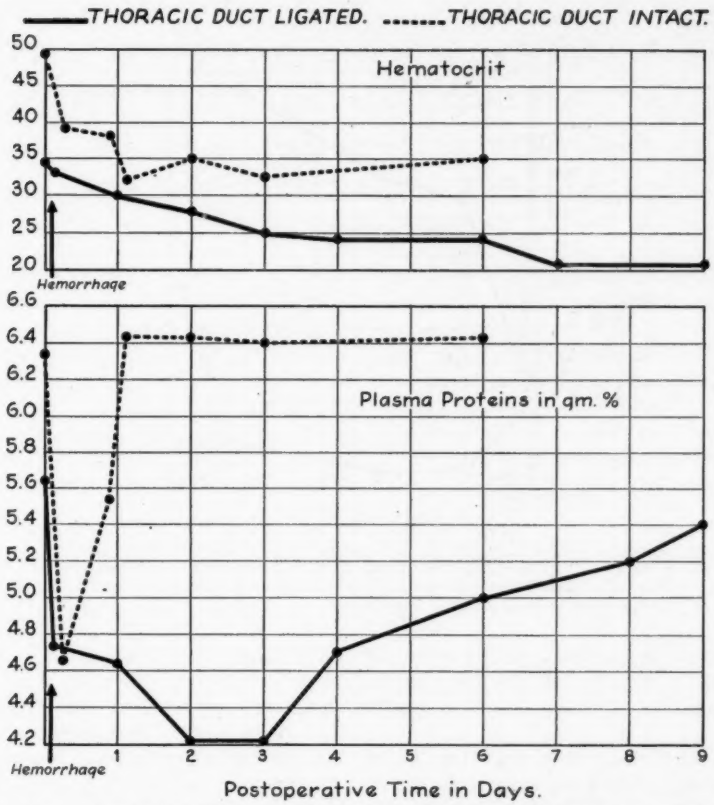

Fig. 1. Graphs illustrating the hematocrit and plasma protein patterns of groups I and II. The solid lines represent the curves of a dog with thoracic duct ligated and the broken line represents the curve of a dog with thoracic duct intact.

first two groups of animals suggests the importance of the thoracic duct in the plasma protein economy of the body. There are 3 explanations for this difference. First, the thoracic duct is the main pathway for (a) the return of proteins from the capillary filtrates back into the blood stream, (b) for the transfer of depot proteins from such important protein depot organs as the liver. The acute blockage of this pathway, therefore, would handicap the return of the plasma protein to a prehemorrhage level. The factor of the development of collateral circulation of the principal lymphatic pathways, as has been shown by Lee to take place in 7 to 14 days, may account for the return to a prehemorrhage level in 8 days or over. The development of collateral circulation may also explain why the 3 dogs in group I, which were again subjected to hemorrhage in 12 weeks, followed the plasma protein curve of the dogs in the control group.

The second explanation is that the ligation of the thoracic duct in some way prevented the absorption of foodstuffs from the alimentary tract, with consequent inability of the animals to replace lost blood proteins. This explanation, however, does not sound plausible for several reasons. In the first place, the work of Whipple (2) and of Weech and their co-workers shows that after plasmapheresis, the plasma proteins are restored from protein reserves in the body, mostly from the liver. In the second place, Van Slyke (5, 6) and

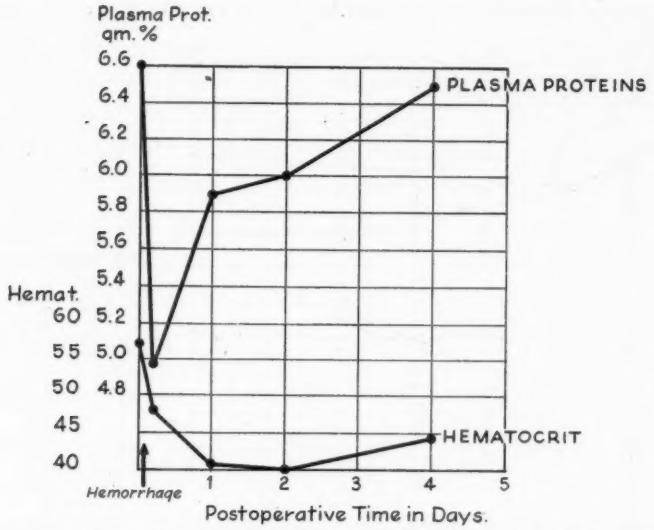

Fig. 2. Graph of hematocrit and plasma protein behavior from same group I dog as in Figure 1, but 12 weeks after ligation and division of thoracic duct. Note the difference between these curves and those of group I, Figure 1; also similarity to those of group II, Figure 2.

Delannay have shown that amino acids are absorbed not by lacteals into the lymphatics, but by capillaries directly into the portal circulation.

The third possible explanation is that blood volume changes in the 2 groups follow two different trends, i.e., following hemorrhage, the thoracic duct ligated animals have a hemodilution for at least 8 days after hemorrhage, while in intact animals, the hemodilution disappears in 48 hours. If this disappearance were the case, the hematocrit values would reflect a similar picture, which in fact did not occur.

SUMMARY AND CONCLUSIONS

The posthemorrhage hematocrit and plasma-protein values were determined in 2 groups of dogs, 1 with the thoracic duct ligated, and the other with the thoracic duct intact.

In the group with the intact thoracic duct, the prehemorrhage level of plasma proteins was achieved in from 24 to 48 hours. In the group with the thoracic duct ligated, this level was not reached until after 8 days.

On the basis of this finding and on the basis of the finding previously reported of increase in protein concentration in thoracic duct lymph following hemorrhage, it is postulated that the thoracic duct, and, therefore, the lymphatic system, is an important pathway not only for the return of proteins from the capillary filtrate to the blood, but also for the mobilization of proteins from protein depots in the body.

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THE LOCAL EFFECT OF TOPIC ANESTHETIC DRUGS ON THE MOTILITY OF THE GASTROINTESTINAL TRACT OF THE HUMAN AND THE DOG

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THE local effects of topic (or local) anesthetic drugs in the treatment of sprains and fractures have been studied extensively by LeRiche and collaborator, and their results have been confirmed by other authors (14, 16). The injection of topic anesthetic drugs into such lesions may diminish or abolish the pain, the swelling, and the reflex contracture. The explanation of this effect is that pain receptors and afferent branches of reflex arcs, including those of axon reflexes, are anesthetized. Thereby, not only pain but also the vicious circle that leads to progressively increasing swelling and rigidity may be abolished

In a manner similar to that noted in the skeletal muscle, the smooth muscle of the gastrointestinal tract may react with spasm to irritants or lesions. The abnormal stimulus may be of various origin: traumatic, mechanical, vascular, thermal, chemical, topic allergic, neurogenic or psychogenic and, experimentally, electrical. In addition to spasm, the abnormal stimulus will produce increased motility in the area affected.

Gastrointestinal motility is regulated by short and long reflex arcs of the sympathetic and parasympathetic nerves and by the myenteric plexuses. Gastrointestinal pain is transmitted largely through the sympathetic nerves; it is usually due to swelling of the submucosa, to overdistention, or to forceful contractions.

The intestines contain local reflex arcs. Bayliss and Starling were the first, 45 years ago, to describe that the action of the musculature of the intestines is in part dependent on the impulses from within the gut itself, "through the intermediation of the local nervous system (Auerbach's and Meissner's plexuses)." Sensory receptors in the mucosa and subserosa connect with the intramural ganglion cells, and these in turn connect with motor fibers to the local musculature. Thus the mechanism for local, intrinsic spasms exists, independent of long nerve connections. Stimulation of the mucosa produces contraction of the overlying musculature, a local myenteric reflex (1, 3, 10, 18, 19). Axon reflexes may also play an important rôle (10).

Attempts have been made to reduce the effects of normal or abnormal stimuli in the gastrointestinal tract, but no systematic work on the effects of topic anesthetic drugs on the motility of the gastrointestinal tract of the intact human or animal has been done as far as we were able to ascertain. The following publications have some bearing on our problem.

Raiford and Mulinos used exteriorized denervated segments of small bowel engrafted into the abdominal wall. Stroking the mucosa of these segments produced muscular contractions. Topical application of cocaine blocked this reflex, but did not alter the muscular response at the same point to a stimulus applied outside the cocainized area. They concluded that cocaine did not prevent contraction of the muscle but abolished the receptivity of the mucosa to mechanical stimuli.

Cohnheim-Kestner and his collaborators have shown that novocainization of a segment of intestinal mucosa abolished reflexes originating from that area (5, 6, 7, 17).

Lenz found that a novocain enema prevented the purgative action of anthraquinone derivatives given by rectum to cats (12).

Bayer reported that larocaine abolished pylorospasm and relaxed the stomach in cases of gastric ulcer by the paralysis of sensory fibers

From the Department of Gastrointestinal Research of Michael Reese Hospital. Aided by a grant from the Nelson Morris Fund. The Department is in part supported by the Michael Reese Research Foundation.

TABLE I.—SUMMARY OF DEGREE AND DURATION OF LOCAL INHIBITORY EFFECTS OF TOPICAL ANESTHETIC DRUGS ON GASTRO-INTESTINAL MOTILITY OF DOGS

	Drugs in mgm.		No. of Expts.	Depression of motility	
				Degree*	Duration, min.
Stomach	Butyn	100	2	0	
	Metycaine	100	1	0	
		200	1	0	
	Trasentine	25	2	0	
		50	3	0	
Duodenum	Butyn	100	1	3+	20–30
		100	1	2–3	
				(T)	30–40
	Diothane	100	1	0	
	Metycaine	50	1	5	20
		100	2	4	15
	Pantocaine	100	2	3(T)	30–40
	Procaine	50	1	3	15–20
		50	1	5	25
		100	2	3	30
	Trasentine	15	1	0	
		15	1	1–2	15–20
	Trasentine 6H	15	2	2	10
Jejunum	Butyn	50	1	1–2(T)	15–30
		100 & 200	2	0(T)	
		200 & 400	2	Spasm(T)	
	Metycaine	10	1	0	
		50	1	0	
		50	1	1	30
		50	1	3	20
		50	5	4	10
	Pantocaine	50	1	2(T)	45–60
	Procaine	50	1	2–3	30
		50	2	4	15
		50	5	5	25
		50	2	5	35
		50	1	5	20–25
	Trasentine	25	1	4–5	25
	Trasentine 6H	25	1	2–3	15
		50	1	0	
		50	1	2–3(T)	30
Ileum	Butyn	200	1	0(T)	
	Metycaine	50	1	2	25–30
		300	1	0	

TABLE I.—SUMMARY OF DEGREE AND DURATION OF LOCAL INHIBITORY EFFECTS OF TOPICAL ANESTHETIC DRUGS ON GASTRO-INTESTINAL MOTILITY OF DOGS—Continued

	Drugs in mgm.		No. of Expts.	Depression of motility	
				Degree*	Duration, min.
Ileum	Procaine	50	1	3	20
		100	1	2	15–20
	Trasentine	2	1	1	30
		5	1	0	
		5	1	1	30
		5	1	1–2	15
		5	1	4	30–40
		10	3	3	45
		15	2	3	50
		50	1	4–5	60–90
Colon	Butyn	200	2	0(T)	
		200	1	4(T)	Permanent
	Metycaine	150	1	0	
	Procaine	150	2	4	30
	Syntropan	10	1	3	30
	Trasentine	10	1	2	15–30

*Degrees of depression.
(1) Questionable effect.
1 Slight drop in tone, height of contraction reduced approximately one-quarter.
2 Drop in tone, height of contraction reduced approximately one-half.
3 Definite drop in tone, height of contraction reduced approximately three-quarters.
4 Definite drop in tone, height of contraction reduced approximately four-fifths.
5 Marked drop in tone, no contractions.
T = Toxic

and local reflex arcs in the gastric mucosa. He reported to have used larocaine successfully in the treatment of acute gastric ulcers.

In a great number of *in vitro* studies on isolated strips of intestine the effects of topic anesthetic drugs have been variable (1, 4, 8, 20, 21), and we feel that the results of *in vitro* experiments have little bearing on our problem.

The work presented here was based on the idea that interruption of reflex arcs in the gastrointestinal tract in conditions of local inflammation and swelling and local pain and spasm could be expected to be beneficial for the same reasons assumed by LeRiche to be beneficial in the case of sprains and fractures. Therefore, the present work was undertaken, the first phase being a study on the effect of

TABLE II.—SUMMARY OF THE LOCAL EFFECTS OF TOPICAL ANESTHETIC DRUGS ON GASTROINTESTINAL MOTILITY OF DOGS

Balloons in:	Metycaine*	Pantocaine	Butyn	Procaine	Trasentine	Trasentine 6H	Diothane Syntropan	Water or Saline
Stomach	o o		o‡		o o o o (+)			o o
Duodenum	++	+††	++	++++		o(+)(+)+	D. +	o o o o
Jejunum	+++++	†	o o (Spasm)	(+)+++++	+	o+†		o o o o o o
	++(+)(+)	†(Spasm)	††	++++++				o o o o o
Ileum	o+		(†)†	(+)++	o(+)(+)(+)+	+		o o o o +
					++++++			
Colon	o			++	+		S. +	o
Total, intestines	2 expts. o		2 expts. o		1 expt. o	2 expts. o		20 expts. o
	2 expts. (+)			2 expts. (+)	3 expts. (+)	2 expts. (+)		
	10 expts. +	1 expt. +	1 expt. +	19 expts. +	9 expts. +	2 expts. +		1 expt. +
		3 expts. +	4 expts. †			1 expt. †		
			1 expt. †					

*Each sign in the columns below the drugs signifies one experiment.
(+)=Questionable inhibition; +=Inhibition; †=Inhibition and toxic effects; o=No inhibition; ‡=No inhibition and toxic effects.

topic anesthetic drugs on gastrointestinal motility.

METHODS

Gastrointestinal motility was recorded with carbontetrachloride-oil (specific gravity 1.5) manometers. Single or double rubber balloons were inserted into the gastrointestinal tract. In the case of a single balloon, used in the tests on the human, a thin catheter was attached to the rubber tube of the balloon, ending just above the balloon; thus, the topic anesthetic drug solutions were injected through the catheter against the balloon. In animal experiments on the intestines, a double balloon system with three tubes was employed. The two balloons were about 1 to 4 centimeters apart and recorded their pressures separately. The third rubber tube opened between the two balloons and, after withdrawal of all fluid possible, the test solution was injected through it; thus the mucosa at the balloons was exposed to the nearly full concentration of the drug. This arrangement yielded more constant results than the single balloon method. In all experiments except one, prolonged control tests without injection of drugs, or with injection of water or 0.9 per cent saline solution were performed, and in the test experiments sufficient control motility was allowed before injection of a drug. In most experiments, gastrointestinal motility was stimulated by marked overdistention of the balloons. In a few experiments on the dog, gastric motility was produced by the subcutaneous injection of small doses of prostigmine. For the study of motility of the stomach only one balloon was used.

In the test on the human, 4 healthy subjects and 2 convalescent patients with a normal gastrointestinal tract was employed. All subjects were in fasting condition. Gastric, duodenal, jejunal, or colonic motility was recorded. The procedure in the tests on duodenal or jejunal motility was similar to that of duodenal intubation, and the position of the balloons was checked by fluoroscopy. In the experiments on the colon, the balloon was introduced through the rectum into the lower sigmoid.

In the first series of experiments on the dog, healthy unanesthetized animals with a metal tube gastrostomy were used for gastric, duodenal, and jejunal motility. All animals were starved for 12 hours before the test but had access to water. The animals had been trained to lie on the table unrestrained, and the taking of rectal temperatures or the giving of intravenous injections did not disturb them. The balloons were introduced through the gastrostomy tube, and their position in the intestine was checked by fluoroscopy. One healthy dog with a cecostomy was used similarly, the

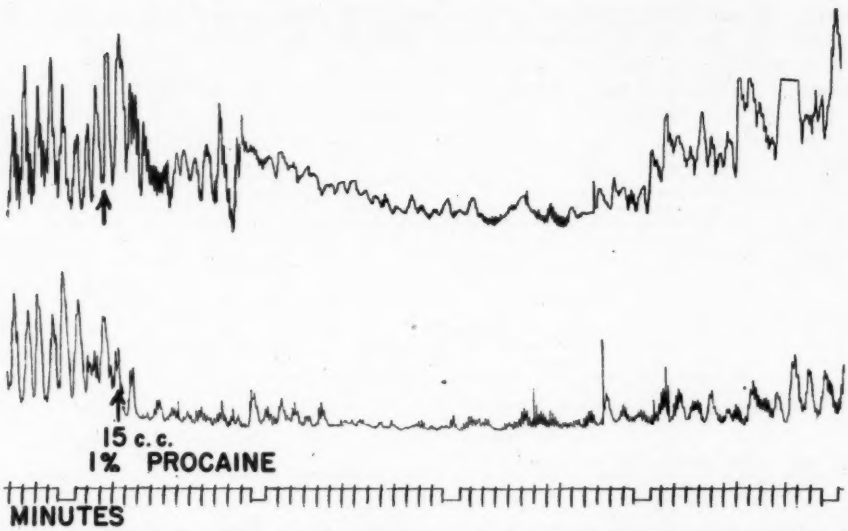

Fig. 1. Colon motility. Unanesthetized, trained normal dog. Two balloons have been introduced into the lower colon through the rectum. Both balloons registered motility separately. The upper tracing is from the proximal balloon and the lower tracing is from the distal balloon. Both balloons were overdistended, and prolonged continuous motility was obtained prior to the administration of the drug. The use of 150 milligrams of procaine in 15 cubic centimeters of water produced an inhibition graded 4 in Table I, lasting approximately 30 minutes.

balloons being introduced into the ileum. In other dogs, the balloons were introduced into the colon through the rectum.

Acute experiments were performed on anesthetized dogs with balloons inserted at various levels of the gastrointestinal tract, taking simultaneous records of the motilities. In these experiments, the solutions of the topic anesthetic drugs were injected either at the balloons or far away from the balloons into a lower segment of the intestine or intravenously, in order to differentiate between their local effects and their effects via the blood stream or by way of long reflex arcs.

In the experiments on the human and on the dog, the drugs to be tested and the water controls were of small volume, between 5 and 40 cubic centimeters of water or saline, and the fluids were warmed before instillation. We had found in the dog, that warming of solutions to about body temperature was essential, because cold solutions would produce intestinal motility at times, which seemed to be due to the temperature of the solution only. The material was instilled slowly in order to avoid effects of sudden distention of the intestine. In a number of chronic experiments on the dog, the test drugs were given also intravenously.

The following drugs were employed: butyn sulfate+, diothane hydrochloride, metycaine hydrochloride, pontocaine hydrochloride, procaine hydrochloride, syntropan phosphate, trasentine hydrochloride, and trasentine 6H.

RESULTS

Experiments on the dog were done first so that a more thorough study could be made on the effectiveness and toxicity of the drugs than was possible in the human. The experimental technique was also developed first in the dog. Human experiments were used to confirm the most important findings. The acute and chronic experiments in the dog have been tabulated together in Table I because the results were similar in both groups. This table shows the doses of the drugs used, the degree and duration of the inhibition obtained, and the site of introduction of the drug in the gastrointestinal tract. Most of the

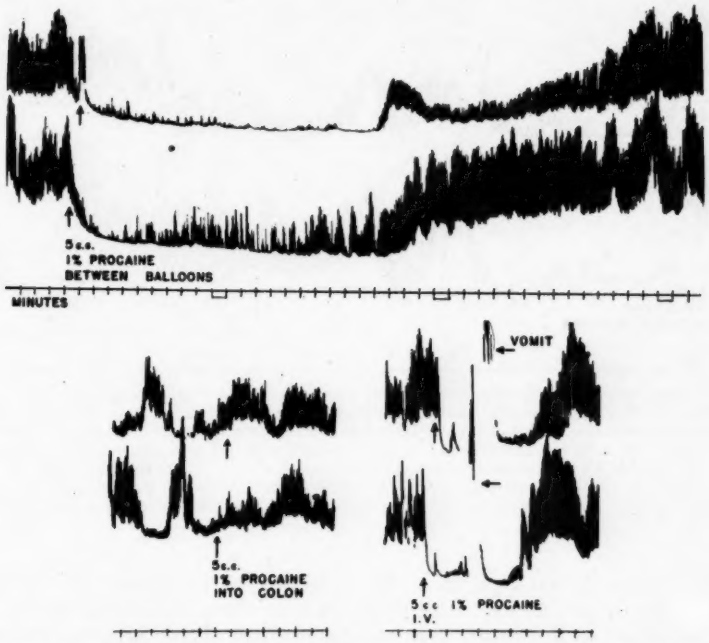

FIG. 2. Jejunum motility. Unanesthetized trained normal dog. Two balloons have been introduced into the jejunum through a gastrostomy cannula. Both balloons registered motility separately. The upper tracing is from the proximal balloon and the lower tracing is from the distal balloon. Both balloons were overdistended, and prolonged continuous motility was obtained prior to the administration of the drug. The administration of 50 milligrams of procaine instilled between the balloons was followed by a distinct drop of tone and depression of motility graded 5, lasting 20 to 25 minutes (see Table III, experiment No. J7). The same dose of procaine instilled into the upper colon through a thin catheter introduced through the rectum had no effect on motility. The intravenous injection of the same dose of procaine was followed by a rather short period of depression of jejunal tone and motility, and the dog was nauseated and vomited. The nausea and the vomiting *per se* may explain the short inhibition of jejunal motility.

drugs tested caused definite inhibition of strong motility in the duodenum, jejunum, ileum, and colon; however, none of the drugs had any effect on gastric motility. In a number of tests, butyn, pontocaine, and trasentine 6H caused toxic reactions consisting of a drop of blood pressure in the acute experiments (fatal in a few animals) and vomiting, restlessness, and excitement in the experiments on the unanesthetized trained dogs. These drugs, therefore, were not used in our tests on the human.

All results on the dog are summarized in Table II. Pontocaine and butyn produced in some experiments spasm of the intestine, either immediately, without a preceding depression, or following a depression of motility. Butyn, in the doses employed, seemed to be most toxic. The drugs which showed no toxic effects and which produced most inhibition of intestinal motility when applied topically were procaine, metycaine, and trasentine. Procaine appeared to be the most reliable drug, as it produced depression of intestinal motility in all experiments. This drug was chosen, therefore, for most tests on the human.

In the last column of Table II, the controls with water or 0.9 per cent saline solution are listed; depression of intestinal motility was seen in only 1 out of 21 tests.

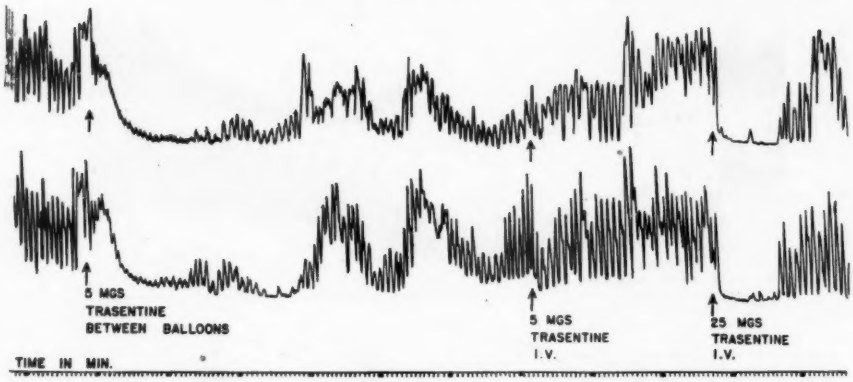

Fig. 3. Ileum motility. Unanesthetized, trained normal dog. Two balloons have been introduced into the ileum through a cecostomy. Both balloons registered motility separately. The upper tracing is from the proximal balloon. Both balloons were overdistended, and prolonged continuous motility was obtained before the administration of the drug. Five milligrams of trasentine instilled between the balloons was followed by distinct drop of tone and depression of motility graded 4 and lasting 30 to 40 minutes (see Table III, experiment No. L8). The intravenous injection of the same dose of the drug had hardly any effect on the ileum motility compared with the effect of local application of the drug at the balloons.

Figure 1 represents a typical experiment on the colon of the unanesthetized dog. One per cent procaine solution to an amount of 15 cubic centimeters was instilled between the balloons and was followed by definite and prolonged inhibition.

A series of experiments was performed in order to analyze the mode of action of the drugs. If we were dealing with a local (topical) surface anesthetic effect, the introduction of the same drug into another segment of the bowel away from the balloons should have no effect on the intestinal motility at the site of the recording balloons. Figure 2 illustrates a typical experiment. Procaine when injected between the balloons recording the jejunal motility produced a marked inhibition of motility, but the same dose of the drug introduced into the colon had no effect on the jejunal motility. However, when procaine was injected intravenously, it produced a toxic inhibition of the motility for a few minutes. This was overcome by the use of a smaller dose of a less toxic drug. Figure 3 shows this in an experiment on ileum motility. A small dose of trasentine produced a marked inhibition of motility when introduced between the balloons and no appreciable effect when the same dose was given intravenously. An intravenous injection of five times the initial dose produced a sharp inhibition, but for a relatively short time. Table III summarizes all the experiments of this type and the data indicate that in every experiment in which a distinct local inhibitory effect was obtained at the site of the balloons, the intravenous injection or the introduction of the same drug into distant parts of the intestine was followed by relatively slight and short inhibition.

The tests on the human were more difficult technically than the animal experiments, because the introduction of the balloons and their retention over prolonged periods of time in order to obtain sufficiently long control tracings, were not successful with each subject. We have been able, however, to perform 10 tests on 6 subjects.

The results were as follows:

Stomach

1. 500 mgm. procaine in 40 c.c. water—no effect.
2. 300 mgm. procaine in 30 c.c. water—no effect.
3. 300 mgm. procaine in 30 c.c. water—drop in tone, motility abolished for 2 hours.

Duodenum

4. 400 mgm. procaine in 20 c.c. of water—distinct drop in tone; motility abolished for 20 minutes.

Jejunum

5. 500 mgm. procaine in 35 c.c. of water—slight depression of motility.

6. 500 mgm. metycaine in 27 c.c. of water—same as above; subject vomited.
7. 500 mgm. procaine in 40 c.c. of water—distinct depression of tone and motility for 30 minutes (see Fig. 3).
8. 750 mgm. metycaine in 30 c.c. of water—no effect.

Colon

9. 20 mgm. procaine in 16 c.c. of water—no effect.
10. 300 mgm. procaine in 15 c.c. of water—abolition of motility for 20 to 30 minutes.

In test No. 3 gastric motility stopped 10 minutes after instillation of the procaine solution and did not return for 2 hours, at which time the test was terminated. In test No. 4 control motility had not been particularly strong. The patient experienced some epigastric pain, apparently from the distended balloon in his duodenum. This pain disappeared following the instillation of the procaine into the duodenum, and it reappeared when duodenal motility had returned 20 minutes later. With one exception, stated above, tone and motility returned to or near control levels when the effects of the drugs wore off. Metycaine was ineffective in one test and produced a questionable inhibition in another test. Vomiting occurred once with 500 milligrams of metycaine.

Figure 4 represents a typical record of inhibition of intestinal motility with procaine (see human experiment No. 7). Following a latent period of approximately 2 minutes, tone and motility were depressed for about 30 minutes.

ANALYSIS

The results reported here demonstrate 3 facts. First, topic anesthetic drugs may produce a local inhibition of intestinal motility and tone. Second, this local motor inhibition may be much stronger than the effect of the intravenous injection or of the introduction of the drug into a distant segment of the intestines. Third, spasmolytic drugs, like trasentine or syntropan, appear to have similar effects, i.e., they may act like a topical anesthetic drug and have a much more pronounced local effect than that following their intravenous injection or their introduction into a distant segment of the intestines.

The local inhibition of intestinal motility with the topical anesthetic drugs probably is affected by anesthesia of the receptors of local reflex arcs, and the consequent abolition of the

TABLE III.—EFFECTS OF LOCAL AND SYSTEMIC ADMINISTRATION OF TOPICAL ANESTHETIC DRUGS

Experiment No.	Drug			Depression of motility	
	In mgm.		Injected into	Degree*	Duration, min.
Duodenal motility (balloons in duodenum)					
A 2 (Acute)	Pantocaine	100	Duodenum	3	30–40
		100	Jejunum	0	
	Butyn	100	Duodenum	2	30–40(T)
		10	Intravenous	0	(T)
		50	Intravenous	0	(T)
A 3 (Acute)	Procaine	50	Duodenum	3	15–20
		100	Duodenum	3	20–30
		100	Ileum	2	15–20
		100	Intravenous	3	15–20
Jejunal motility (balloon in jejunum)					
J 7 (Chronic)	Procaine	50	Colon	0	
		50	Jejunum	5	20–25
		50	Intravenous	(1)	5–6(T)
		50	Colon	0	
J 8 (Chronic)	Procaine	50	Jejunum	4	15
		50	Ileum	0	
		50	Intravenous	(1)	2(T)
		50	Jejunum	4	15
Ileum motility (balloon in ileum)					
L 8 (Chronic)	Trasentine	5	Ileum	4	30–40
		5	Intravenous	0	
		25	Intravenous	4	10
L 11 (Chronic)	Trasentine	15	Ileum	3	40–60
		15	Intravenous	3	15
L 13 (Chronic)	Trasentine	15	Ileum	3	30–40
	Trasentine 6H	15	Intravenous	3	10–15
Colon motility (balloon in colon)					
C 3 (Chronic)	Trasentine	10	Colon	2	15–30
		10	Intravenous	2	15–20
C 4 (Chronic)	Syntropan	10	Colon	3	20
		10	Intravenous	0	

* Degrees of depression.
(1) Questionable effect.
1 Slight drop in tone, height of contraction reduced approximately one-quarter.
2 Drop in tone, height of contraction reduced approximately one-half.
3 Definite drop in tone, height of contraction reduced approximately three-quarters.
4 Definite drop in tone, height of contraction reduced approximately four-fifths.
5 Marked drop in tone, no contractions.
T=Toxic.

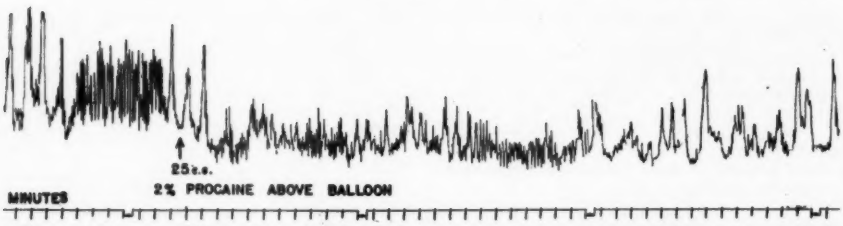

Fig. 4. Jejunum motility. Normal male subject, 19 years of age, 130 pounds in weight. A single balloon was introduced through the mouth. Its location in the jejunum was confirmed by fluoroscopy. Twenty-five centimeters of a 2 per cent procaine solution was injected through a thin catheter attached to the balloon tube and ending just above the balloon. The tube was then rinsed with 15 centimeters of water. Note marked drop in tone and motility.

expulsion reflex produced by the distended balloon. This effect must be a local one, because the drug did not seem to act as effectively from the blood stream following its intravenous injection. The absence of, or the slight effect following, the introduction of the drug into a distant caudal segment of the intestine shows that we were not dealing with depression of motility through long reflex arcs, or through absorption of the drug into the blood or lymph.

The topic anesthetic effects of some of the spasmolytic drugs have been described (9, 15), but nobody to our knowledge, has associated their spasmolytic effect with that of topical anesthesia. If this work can be extended and confirmed we may have to change some of our concepts about the mechanism of action of these drugs.

Our findings may have clinical application. With a Miller-Abbott tube in place above the site of obstruction of a spastic ileus, the instillation of procaine or trasentine solution may be tried, and the spasm may be relieved. If we think in the terms of the vicious circle associated with sprains, described herein, we may also expect a prevention or diminution of swelling of the intestinal mucosa.

We are not able to explain why in no animal experiment, and in only one test on the human, was gastric motility depressed. It is possible that the sensory innervation of the gastric mucosa is different from that of the intestinal mucosa.

SUMMARY

The effects of topical anesthetic drugs were studied on gastric and intestinal motility and tone of the human and of the dog.

Intestinal motility and tone were inhibited in a great number of tests following the local application of such drugs.

Gastric motility was inhibited in only one test in a human subject, and in none of the experiments on the dog.

Certain spasmolytic drugs have a distinct topical anesthetic effect on the intestinal mucosa, similar to that of the well known topical anesthetic drugs.

The local inhibition of intestinal motility and tone by the topical anesthetic drugs and by some spasmolytic drugs is not due mainly to effects via the blood stream or via long reflex arcs, but is due mainly to local action, apparently anesthesia of sensory receptors and abolishment of local motor and tone reflexes.

The possible clinical application of the results observed is discussed.

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THE RELATION OF VITAMIN C TO ANESTHESIA

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IN the course of a study concerning the protective action of vitamin C against liver damage (2) it was observed that the state of vitamin C nutrition of guinea pigs materially influenced their response to certain anesthetics which were used as hepatotoxins. Except for one indefinite report (12) a review of the literature revealed no publications dealing directly with the effect of anesthesia on the vitamin C content of blood plasma or the effect of vitamin C deficiency on the response of an animal to anesthesia.

The purpose of this research was to determine (1) the effect of anesthesia on the vitamin C content of plasma, and (2) the effect of C avitaminosis on the animal's response to anesthetic agents.

PROCEDURE

The vitamin C content of plasma was determined by the photocolorimetric method of Mindlin and Butler. Six to 8 cubic centimeters of blood was drawn, centrifuged, and 2.5 cubic centimeters of plasma used for the analyses. Care was exerted in drawing the samples to avoid hemolysis, the presence of which quickly decreased the apparent ascorbic acid content of plasma. These determinations were made immediately after the blood was drawn, for in our experience the vitamin C content of whole blood from the dog decreased on standing even a few hours at 5 degrees C. Samples of blood for analysis were drawn according to the following schedule: (1) immediately before an induction to serve as controls, (2) just before a 45 minute anesthetization was terminated, (3) 5 to 7 hours after an experiment was begun, and (4) a final sample 24 hours after the induction. Additional determinations of plasma C were made 48 hours after anesthesia in one set of experiments.

The anesthetics used in the course of these experiments were diethyl ether, vinethene,[1] chloroform, and cyclopropane. The first three agents were given by the "open drop" technique to 8, 6, and 12 dogs, respectively. The animals used for the "open drop" anesthetizations were not intubated. None of the animals used in these experiments was given any type of premedication. All the dogs were maintained at light surgical anesthesia for 45 minutes.

Six dogs were anesthetized by rebreathing a cyclopropane-oxygen mixture from a 5 liter rubber bag. They were then fitted with a cuffed endotracheal tube to insure an open airway, and were connected through a soda-lime carbon dioxide absorbing cannister to a 100 liter rubber bag containing a 25 per cent mixture of cyclopropane in oxygen. The animals were maintained on this anesthetic mixture for 45 minutes. In unpremedicated dogs this concentration of cyclopropane produced light surgical anesthesia. Six other animals were anesthetized in the same manner but were maintained for 45 minutes on a mixture of 25 per cent cyclopropane, 10 per cent oxygen, and 65 per cent nitrogen.

Closed system anesthesia with diethyl ether was employed for 12 animals. Induction was

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[1]Trademark of Merck & Co. for divinyl ether.

brought about by the "open drop" technique. After intubation the animals were connected through a soda-lime cannister to the anesthetic reservoir which was a Tissot spirometer of 100 liters' capacity. Six of the dogs were maintained for 45 minutes on a 4 per cent mixture of ether in oxygen; and the other 6 maintained for the same period of time on a mixture of 4 per cent ether, 10 per cent oxygen, and 86 per cent nitrogen. This concentration of ether also produced light surgical anesthesia in unpremedicated dogs. The concentrations of the gases were checked repeatedly by analysis.

To study the effect of the vitamin C content of an animal on its response to anesthesia, guinea pigs were used. These were divided into 2 groups. Both groups were placed on a diet of purina rabbit chow checkers[1] known to be deficient in vitamin C but otherwise adequate. Ecker and Pillemer have reported that on this diet guinea pigs showed signs of scurvy in 21 days and that 10 to 20 milligrams of ascorbic acid per day was necessary to maintain optimal plasma concentration of the vitamin. One group was given no vitamin C. The other group of guinea pigs was given 30 milligrams of ascorbic acid daily. The ascorbic acid was made up with half its weight of sodium bicarbonate, dissolved in 1 cubic centimeter of distilled water and immediately injected subcutaneously. The weight of the guinea pigs in each group was followed for about 16 days, at which time the deficient animals ceased to gain. At that time the effect of an anesthetic on the animals of both groups was studied. A glass chamber of approximately 15 liters' capacity was used for these experiments. This was provided with an adequate inlet and outlet for air, the anesthetic being volatilized in the chamber. Vinethene, ether, and chloroform were the anesthetics used.

A comparison of the response of vitamin C deficient and adequate animals was made by placing guinea pigs of each group in the induction chamber at the same time and comparing their reaction to the anesthetic agent. While it would be difficult to control the experiment by direct "open drop" anesthesia, one can compare by this method the responses of two groups of animals at the same concentration of the volatile agent. The period of anesthetization varied from long enough to induct the deficient guinea pigs to 45 minutes, depending on the comparison to be noted.

[1] The composition of the diet was as follows: protein 15.35 per cent; fat 2.38 per cent; carbohydrates 64.61 per cent (including 16.86 per cent fiber); calcium carbonate; phosphorus; sodium chloride; potassium iodide, magnesium sulfate, and per pound (0.5 kgm.) approximately 5,000 international units of vitamin A, approximately 400 international units of vitamin B_1, approximately 3,000 micrograms of riboflavin (B_2) and negligible vitamin C.

RESULTS

The effect of anesthesia on plasma vitamin C. A low control plasma level of ascorbic acid seemed characteristic of dogs maintained on a diet of purina dog chow which was practically devoid of vitamin C. The average of the control values (omitting the B dogs of the vinethene series) listed for 46 dogs was 0.359 milligram per 100 cubic centimeters. It was possible to increase the plasma vitamin C level by the subcutaneous administration of 150 milligrams of ascorbic acid daily for several days as was done for the dogs lettered "B" of the vinethene series (Table I).

In general, the effect of anesthesia was first to increase the vitamin C concentration in plasma within 7 hours following induction and then to lower its level below the control values within 24 hours. This generalization holds for vinethene, chloroform, ether, and cyclopropane uncomplicated by inadequate oxygenation (Tables I and II). From this trend the effects of the different anesthetics vary somewhat.

The actual or real increase in plasma vitamin C expressed in milligrams per 100 cubic centimeters of plasma was on the whole, but not invariably, independent of the initial plasma concentration. For this reason, 2 dogs having quite dissimilar control plasma C values but whose mobilization was the same in amount after the period of anesthesia showed a markedly different per cent increase over the control levels. Reflection will make it apparent, then, that per cent increase rather than actual increase would be a hazardous basis for the interpretation of these results. Consequently, throughout this paper comparisons will be made of the actual increase (mgm. per 100 c.c. of plasma) though the per cent increase is also given in the tables.

Following anesthesia produced by vinethene, some of the animals mobilized ascorbic acid

into the plasma more readily than did others, but most of them had their highest reading within 5 to 7 hours following the induction (Table I). In only one animal did the plasma vitamin C continue to rise for 24 hours. There was noted an initial fall in the ascorbic acid content of the plasma in 3 of the 12 dogs. Actually, these data represent but single determinations on a number of animals though we have done repeated experiments on each of them. This initial fall was occasionally seen in most of the dogs of this group and may be a part of the response in all of them.

In the case of chloroform (Table I) the mobilization of vitamin C into the plasma seemed to be much more rapid, being greater at the end of the induction in two-thirds of the animals than at the later period. The mobilization of reduced vitamin C into the plasma under influence of vinethene was greater than in the case of chloroform anesthesia (0.237 mgm. per 100 c.c. as compared with 0.175 mgm. per 100 c.c.). Also the fall within 24 hours was greater for vinethene than for chloroform (0.214 mgm. per 100 c.c. as compared with 0.083 mgm. per 100 c.c.). We do not feel justified in making more than this qualitative distinction between the two compounds in this matter because of the marked difference in the average control levels of ascorbic acid in the two series. Chloroform has been known for many years to be quite toxic. Orth, Slocum, Stutzman, and Meek reported the hepatotoxic effect of vinethene. The greater degree of liver damage following vinethene than after chloroform anesthesia which they observed may explain the apparently greater upset of ascorbic acid metabolism in the case of vinethene.

While ether anesthesia does produce a transient hyperglycemia and glycosuria, both ether and cyclopropane are generallyconsidered fairly innocuous so far as after-effects are concerned. However, from Tables I and II it is evident that the mobilizing effect of ether on plasma ascorbic acid was greater by both "open drop" and closed system administration than for either chloroform or vinethene. The average of the maximal increase following "open drop" ether anesthesia was 0.298 milligram per 100 cubic centimeters which was greater than the mobilization effect of vinethene (0.237 mgm. per 100 c.c.) and 75 per cent greater than for chloroform (0.175 mgm. per 100 c.c.). On the other hand, the average fall below normal (0.158 mgm. per 100 c.c.) 24 hours after ether anesthesia was between the corresponding values for chloroform and vinethene (0.081 and 0.214 mgm. per 100 c.c., respectively). The rate of mobilization of plasma vitamin C was slower following ether than following chloroform and is comparable to the rate of increase following vinethene, to which agent it is more closely related chemically.

Cyclopropane anesthesia was followed by the least rise in plasma vitamin C (0.131 mgm. per 100 c.c., average), and this occurred at the end of the period of anesthesia. The fall of the plasma level below normal after 24 hours (0.187 mgm. per 100 c.c.) was somewhat greater than for ether.

Closed system anesthesia with both cyclopropane and ether was undertaken to evaluate the part inadequate oxygenation might play in the results (Table II). While with the "open drop" technique the dogs were kept in light surgical anesthesia and apparently well oxygenated, we believed that our results might possibly be interpreted as being due to inadequate oxygen supply to the animals.

In a comparison of two groups of cyclopropane anesthetizations in which 75 and 10 per cent oxygen was supplied, certain differences were evident. When a high percentage of oxygen was used the mobilization of vitamin C was immediate. The plasma C level then fell off to below the controls at the end of 24 hours. In the case of the dogs administered 10 per cent oxygen in the anesthetic mixture the rise in plasma C levels increased more gradually and persisted over 24 hours, falling to or about the control levels only after 48 hours. A secondary fall in plasma ascorbic acid level did not characteristically occur within 2 days. When 10 per cent oxygen was administered with the same amount of cyclopropane as before, nitrogen being used as the diluent, the animals were deeply cyanotic during the whole of the anesthetization and had to be watched carefully to avoid acute cardiac failure. There seemed to be an increased fragility of the cells for there was experienced considerable diffi-

TABLE I.—THE EFFECT OF 45 MINUTES OF VINETHENE, CHLOROFORM, AND DIETHYL ETHER ANESTHESIA, OPEN DROP ADMINISTRATION, ON THE PLASMA VITAMIN C LEVEL OF DOGS

Dog	Plasma vitamin C in mgm. per cent								
	Control	Period 1	Period 2	Period 3	Maximal increase			Decrease	
		End of anesthesia	5–7 hrs. after induction	24 hrs. after induction	Actual mgm.	Per cent	Period	Actual mgm.	Per cent
Vinethene									
1A	0.258	0.413	0.568	0.181	0.310	120.0	2	0.077	29.8
2A	0.323	0.258	0.583	0.276	0.260	80.5	2	0.047	14.5
3A	0.553	0.735	0.468	0.259	0.182	33.1	1	0.294	53.3
4A	0.412	0.528	0.412	0.146	0.116	28.2	1	0.266	64.7
5A	0.290	0.224	0.690	0.213	0.400	138.0	2	0.077	26.5
6A	0.223	0.181	0.249	0.327	0.104	46.7	3	0.000	00.0
7A	0.287	0.296	0.447	0.255	0.160	55.8	2	0.032	11.2
8B	0.908	0.962	1.080	0.298	0.172	19.0	2	0.610	67.2
9B	1.050	1.380	1.520	0.613	0.470	44.7	2	0.437	41.6
10B	0.807	1.000		0.153	0.193	24.0		0.654	81.2
11B	0.271	0.500	0.388	0.213	0.229	84.5	1	0.058	21.4
12B	0.526	0.773	0.680	0.502	0.247	47.0	1	0.024	4.6
Average	0.492				0.237	60.1		0.214	34.7
Chloroform									
13	0.431	0.610	0.364	0.256	0.179	41.6	1	0.175	40.7
14	0.274	0.249	0.341	0.205	0.067	24.4	2	0.069	25.2
15	0.240	0.358	0.188	0.037	0.118	49.2	1	0.203	84.6
16	0.048	0.222	0.188	0.025	0.174	363.0	1	0.023	47.9
17	0.145	0.248	0.287	0.117	0.142	98.0	2	0.028	19.3
18	0.144	0.513	0.213	0.490	0.369	256.0	1	0.000	00.0
Average	0.214				0.175	138.7		0.083	36.3
Ether									
19	0.294	0.492	0.316	0.020	0.198	67.4	1	0.274	93.2
20	0.570	0.468	1.255	0.284	0.685	120.0	2	0.286	50.2
21	0.447	0.597		0.447	0.150	33.6		0.000	00.0
22	0.519	0.510	0.791	0.137	0.272	52.4	2	0.382	73.7
23	0.046	0.136	0.213	0.082	0.167	363.0	2	0.000	00.0
24	0.153	0.144	0.622	0.069	0.469	306.5	2	0.084	54.9
25	0.222	0.282	0.513	0.041	0.291	131.0	2	0.181	81.5
26	0.196	0.348		0.136	0.152	77.7		0.060	30.6
Average	0.306				0.298	143.9		0.158	48.0

culty in drawing blood at the 5 to 7 hour interval after anesthetization without obtaining some hemolysis which would of course produce error in the results. However, among these animals only 3 had an apparent mobilization peak at the end of anesthesia. It was observed (Table II) that in the case of these the blood drawn at the 5 to 7 hour period was hemolyzed

to some extent, consequently the values they represented were probably too low. The extent of the delayed rise in the animals maintained at low oxygen tension during anesthesia was not significantly different from the extent of the rise when 75 per cent oxygen was used. In the case of cyclopropane it was concluded that the immediate mobilization and the fall below the control plasma vitamin C after 24 hours was initiated by the anesthetic agent, not by insufficient oxygenation.

Likewise, in closed system ether anesthesia oxygen deficiency was ruled out as a factor in production of the vitamin C effect. In all of the ether experiments, the dogs supplied with 96 per cent oxygen, those supplied with air ("open drop") and others with 10 per cent oxygen, the maximal mobilization of ascorbic acid was in 5 to 7 hours following induction. If inadequate tissue oxygenation were responsible for the initial rise and subsequent fall in plasma vitamin C one would expect the greatest effect when only 10 per cent oxygen was administered and least change with the mixture containing 96 per cent oxygen. Actually, the reverse was true. The greatest mobilization of the vitamin was in the experiments in which 96 per cent oxygen was given with ether, next greatest in the "open drop" experiment, and least mobilization of plasma C when 10 per cent oxygen was supplied and the dogs remained deeply cyanotic for 45 minutes. The fall of the plasma C levels below the control values was about the same for dogs anesthetized by the "open drop" and the closed system containing 96 per cent oxygen in the gas mixture. Again, the fall was least in the case of the dogs rendered cyanotic. These comparisons are based on the actual increase or decrease in the content of ascorbic acid in 100 cubic centimeters of plasma (mgm. per cent) (Tables I and II).

The effect of vitamin C deficiency on the response of guinea pigs to anesthesia is more easily described than expressed in tabular form. Forty-two guinea pigs prepared for the experiments in the manner described in the procedure were divided into three groups: (1) 8 adequate and 8 vitamin C deficient guinea pigs were used for the chloroform anesthetizations; (2) 7 adequate and 7 deficient animals were used for vinethene; and (3) 6 adequate and 6 vitamin C deficient guinea pigs were used for ether anesthetizations. All of the guinea pigs had been on the same basal diet. Representative protocols of the experiments serve to illustrate the effect of the anesthetics on the animals. For any one experiment the concentration of the anesthetic was, of course, the same for all the animals.

Protocol 1. Ether anesthesia. Animals 1 and 2 of the vitamin C deficient and adequate guinea pig groups were used. When placed in the anesthetization chamber the C deficient animals fell over on their side and became unconscious 5 minutes before those that had received vitamin C. The deficient pigs were much more deeply anesthetized as judged by movements and respiration. After 30 minutes' anesthetization the animals having received ascorbic acid were able to right themselves 10 to 15 minutes sooner than the C deficient animals. The avitaminotic animals were in poor condition 18 hours after anesthesia. The number 2 deficient guinea pigs died within 24 hours following anesthesia.

Summary: With the use of a slowly induced, prolonged ether anesthesia, vitamin C deficient guinea pigs became anesthetized sooner, were more deeply anesthetized, and recovered more slowly than the C injected animals. The deficient animals showed prolonged toxic manifestations after the period of anesthetization.

Protocol 2. Chloroform anesthesia. Animals 7 and 8 of the vitamin C adequate and deficient groups were used. The deficient guinea pigs were anesthetized the more quickly and within 5 minutes went into respiratory arrest from which they could not be revived. During this time the number 8 C adequate animal became very lightly anesthetized and the number 7 ascorbic acid injected guinea pig did not fall off its feet. Both of these animals apparently recovered completely 5 minutes after a 10 minute period of anesthesia.

Summary: With the use of rapid induction chloroform anesthesia the vitamin C deficient guinea pigs became anesthetized sooner and died at a concentration of the anesthetic agent which produced partial to light anesthesia in the vitamin C injected animals.

Protocol 3. Vinethene anesthesia. Animals 6 and 7 of the vitamin C adequate and deficient groups were used. The concentration of the anesthetic agent was very carefully controlled so that the C adequate guinea pigs were lightly anesthetized, the C deficient animals being much more deeply anesthetized. After a simultaneous 45 minute period of anesthesia for

TABLE II.—THE EFFECT OF 45 MINUTES OF CLOSED SYSTEM CYCLOPROPANE AND ETHER ANESTHESIA, WITH AND WITHOUT ADEQUATE OXYGENATION, ON THE PLASMA VITAMIN C LEVEL OF DOGS

Dog	Plasma vitamin C in mgm. per cent									
	Control	Period 1	Period 2	Period 3	Period 4	Maximal increase			Decrease in 24 hrs.	
		End of anesthesia	5–7 hrs. after induction	24 hrs. after induction	48 hrs. after induction	Actual mgm.	Per cent	Period	Actual mgm.	Per cent
Cyclopropane 25%, oxygen 75%										
27	0.430	0.650	0.526	0.287		0.220	51.2	1	0.143	33.3
28	0.289	0.381	0.161	0.000		0.092	31.9	1	0.289	289.0*
29	0.535	0.741	0.526	0.430		0.206	38.6	1	0.105	19.7
30	0.212	0.396	0.205	0.036		0.184	87.0	1	0.176	83.1
31	0.446	0.509	0.413	0.361		0.063	14.1	1	0.085	19.1
32	0.526	0.313sh	0.544	0.390		0.018	3.4		0.136	25.9
Average	0.406					0.131	37.7		0.156	36.2
Cyclopropane 25%, oxygen 10%, nitrogen 65%										
33	0.230	0.230	0.265	0.412	0.254	0.182	79.1	3	0.000	00.0
34	0.422	0.382	0.397	0.631	0.338	0.209	49.5	3	0.000	00.0
35	0.364	0.524	0.331sh	0.452	0.524	0.160	44.0	4	0.000	00.0
36	0.331	0.478	0.352h	0.313	0.346	0.147	44.4		0.018	5.4
37	0.348	0.635	0.000h	0.570	0.508	0.287	82.5		0.000	00.0
38	0.413	0.195h	0.446	0.194	0.246	0.033	8.0	2	0.219	53.0
Average	0.351					0.169	51.2			
Ether 4%, oxygen 96%										
39	0.460	0.571	0.775	0.338		0.315	68.5	2	0.122	26.5
40	0.404	0.632	0.468	0.194		0.228	56.5	1	0.210	52.0
41	0.500	0.363h	1.065	0.404		0.565	113.0	2	0.096	19.2
42	0.444	0.556	0.948	0.396		0.504	113.4	2	0.048	10.8
43	0.625	0.372sh	0.640	0.412		0.015*	2.4*	2	0.213	34.1
44	0.602	0.428	1.191	0.663	0.451	0.589	97.8	2	0.151	25.2
Average	0.506					0.440	89.8		0.140	27.9
Ether 4%, oxygen 10%, nitrogen 86%										
45	0.428	0.362	0.687	0.313		0.259	60.6	2	0.115	26.9
46	0.508	0.404	0.662	0.279		0.154	30.3	2	0.229	45.0
47	0.508	0.782	0.840	0.555		0.332	65.3	2	0.000	00.0
48	0.374	0.246	0.394	0.313		0.020*	5.4*	2	0.061	16.3
49	0.524	0.508	0.629	0.346		0.105	20.0	2	0.178	34.0
50	0.399	0.492	0.807	0.617		0.408	102.3	2	0.000	00.0
Average	0.457					0.252	55.7		0.097	20.4

*Not included in average.
sh—slightly hemolyzed.
h—hemolyzed.

both groups, the animals receiving ascorbic acid recovered and were apparently normal in 20 minutes. The avitaminotic animals made a slower partial recovery but were dead the next morning, after 18 hours.

For purposes of illustration each experiment was herein represented by a different anesthetic agent. The same observations held qualitatively for all 3 agents, ether being apparently the least toxic of the 3 anesthetics to the vitamin C deficient guinea pigs.

To sum up these experiments, it has been observed that vitamin C deficient guinea pigs not yet showing any manifestations of scurvy (unless cessation of weight gain be considered a sign) were more quickly inducted by a given concentration of ether, chloroform or vinethene, were more deeply anesthetized and recovered more slowly, if at all, than animals that had been injected daily with an adequate amount (30 mgm.) of ascorbic acid.

ANALYSIS OF STUDY

The initial mobilization and secondary depletion of plasma ascorbic acid which we observed fits in with the results of others to give an attractive composite picture of the effect of anesthesia on the distribution and excretion of vitamin C. This overall phenomenon can be depicted clearly from available data without the need for speculation as to the more fundamental processes involved.

Our data indicate that the ascorbic acid content of plasma does increase during, and for at least 7 hours following, anesthetization, when any of several agents is used. This effect is qualitatively independent of the mode of induction and the presence of adequate or inadequate oxygenation (Tables I and II). It is interesting to recall at this point that Sherry, Friedman, Paley, Berkman, and Ralli showed by simultaneous creatinine and ascorbic acid clearances that the tubular reabsorptive mechanism for the vitamin is limited by a low maximal rate so that as the filtration rate exceeds this maximum the excess is excreted in the urine. One would anticipate, then, that as the plasma vitamin C level increases following anesthesia the urinary output of ascorbic acid would increase. Actually, this has been found to be true. In 1935 Zilva noted that when ether was employed for intravenous injection of vitamin C into guinea pigs the excretion of the vitamin was twice as great as when administered under novocain. Milhorat, Bartels, and Toscani, and Bersin, Lauber, and Nafziger have also reported an increased urinary ascorbic acid output following chloroform anesthesia.

The mobilization of vitamin C for repair (5) as the tissues recover from the depressive action of anesthesia on cellular respiration (11) serves as a second factor to deplete the plasma of the vitamin. When the increased excretion and tissue utilization following anesthesia are considered it is quite consistent that we should have found the plasma ascorbic acid levels to be reduced 27.9 to 48.0 per cent below the preinduction levels 24 hours after anesthesia. Reflecting this same process are the data of Bowman and Muntwyler. They found that for the first 24 hours after a 2 hour ether anesthetization the ascorbic acid excretion by dogs increased 2 to 5 times. However, during the second postanesthesia 24 hour period the vitamin C output was below the preinduction control periods.

Finally, clinical corroboration of these experimental observations on dogs may be deduced from the report by Lund. His data show that within the first 2 postoperative days the plasma ascorbic acid level of patients decreased 30 to 50 per cent and remained low for at least 4 days or until the patient's recovery. It is likely that the depletion of plasma vitamin C by repair of surgical trauma is an exaggeration of the fall in plasma ascorbic acid found to occur 24 hours after an induction.

We appreciate that several important aspects of the problem remain unanswered. It is apparent that ascorbic acid is readily released from some source under the influence of anesthesia but we can offer no explanation from our data as to how it is contained in or released by tissues. While inadequate tissue oxygenation is not responsible for the mobilization or depletion of the plasma vitamin C level it does somehow quantitatively influence the extent of these phenomena, tending to diminish both fluctuations. We have limited our discussion of the increased excretion of the vitamin with increased blood level to the con-

commitant increase in filtration rate, realizing that tubular resorption of vitamin C is very likely influenced by anesthesia also.

We can only speculate as to the cause of the exaggerated response of vitamin C deficient guinea pigs to anesthesia. Malmberg and Euler have reported that depriving guinea pigs of ascorbic acid for 3 weeks diminished the vitamin C content of the brain to 1/5 of the normal value. The sensitization to anesthetization by vitamin C deficiency may or may not be but a part of a general decrease in functional capacity of all organs. We have found that an adequate supply of ascorbic acid protected guinea pigs from hepatic damage and discussed in a previous report the relation of the vitamin to hepatic function (2).

SUMMARY

During and at least for the first 7 hours following a 45 minute period of anesthesia the dog plasma ascorbic acid level increased markedly. Subsequently the plasma level fell within 24 hours to below the preinduction control levels. These observations held for cyclopropane, ether, vinethene, and chloroform independently of the mode of anesthetization. This effect was due to the anesthetic agent and not to an inadequate oxygen intake which tended only to reduce the rate and extent of the mobilization and to decrease or abolish the 24 hour fall in plasma ascorbic acid level.

The increase and subsequent depletion of plasma vitamin C levels have been discussed as part of a proposed concept of the overall effect of anesthesia on the distribution and excretion of the vitamin.

Vitamin C deficiency caused guinea pigs to be more quickly inducted into a state of anesthesia and more profoundly depressed by a given concentration of ether, chloroform, or vinethene. The vitamin C deficient animals recovered slowly if at all from a duration of anethesia which had little apparent after-effect on guinea pigs that had received the same scorbutogenic diet but which were injected with 30 milligrams ascorbic acid daily.

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RECONSTRUCTION OF THE COMMON BILE DUCT

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IT has ever seemed to me that the greatest service a surgeon can make to the progress of the art and science of surgery is to discuss the difficulties he has met with in practice. It has been said that the chief function of an experienced surgeon is to make a difficult operation easy and in no operation is this more true than in that of cholecystectomy. Every removal of a gall bladder, easy though it may seem, is fraught with very great danger and one small error may convert a patient with a mild disability into one in immediate danger of death or of prolonged misery, and many subsequent operations, which at best may only give an incomplete life.

How great is the tragedy and misery which may arise from such errors is exemplified by the following 2 cases from my series:

CASE 45. A medical practitioner aged 58 years, after a long and useful life ministering to the sick of a busy practice and much beloved by his large circle of friends and patients, was about to retire to the country to pass in peace and happiness the evening of his life, enjoying a well earned rest and pleasantly occupied with his hobbies and the visits of his friends. He was still in good health and able to enjoy an active life. He began to suffer, however, with flatulent dyspepsia and occasional attacks of severe pain. Believing that he had gall stones he thought to have advice before retiring and consulted a London surgeon. His diagnosis was confirmed, operation was advised and performed in 1921. The details of the operation were not available but it is known that the gall bladder was removed with one large stone. For 6 weeks after the operation there was a persistent fistula and attacks of colic. Three months later jaundice made its appearance. A second operation was performed by another London surgeon, but after it there was continuous pain and frequent attacks of jaundice and rigors, the jaundice later becoming persistent. When I saw him in 1924 he was thin and wasted. There was a gray green jaundice with complete absence of bile from the stools. There were frequent rigors with attacks of severe colic and the liver was enlarged and tender. The skin showed widespread excoriations due to his constant attempts to relieve the intolerable itching. He was in profound misery and he had become a confirmed morphine addict. At operation there were widespread and dense adhesions but after prolonged dissection the portal vein and the hepatic artery were laid bare in their whole length. No trace of a duct could be found, however. An opening was made in the liver and a tube inserted but no bile escaped. He lingered on for a while taking large doses of morphine but died at the end of a year. A life which should have ended in several years of well deserved peace, happiness and comfort was converted into one of pain, misery and hopelessness.

CASE 33. In a pleasant suburb of a large south coast town there lived in 1936 a well developed, pretty and attractive girl of 21. She had been happily married for a little over a year to a young man who held a post in the shore establishment of the Navy and was certain of advancement. She had a baby son and lived in a small house in a congenial neighborhood surrounded by her friends. Having domestic help she spent her days in the enjoyment of her household duties and of her garden, rejoicing in the affection of her husband and child. Her life was one of happiness and laughter and her future seemed assured. In February of that year she had one day a sudden severe attack of pain in the upper abdomen. It soon passed off and she paid but little attention to it. It was, however, the small black cloud which at first no larger than the palm of a man's hand grew and grew until for 7 years it filled her whole horizon. The attacks returned and increased in frequency and severity. In April she saw her family doctor who advised operation. He operated himself, removed the appendix, and drained the gall bladder. There was no relief from the attacks of pain and in April, 1937, he operated again and removed the gall bladder. It was said to contain one stone. A fistula formed and persisted for a long time and the day following the operation she became jaundiced for the first time. The jaundice continued with periodic remissions as the discharge from the fistula increased. In 1940 a provincial surgeon was called in who carried out an operation said to consist of restoration of the divided duct. It was unsuccessful and her life became one of long continued misery and pain but her spirits kept up and she continued her duties between the attacks and resolutely refused to take narcotics for relief.

In April, 1942, she was seen by a London surgeon who operated upon her in a hospital in London. Some details of this operation were obtainable; it was said that the duodenum was opened and an attempt was made to dilate the duct from below. During this procedure the duct in part tore away from the liver. She recovered from the operation but the jaundice persisted. She was told that nothing further could be done. Her condition became most miserable with constant pain, jaundice, and irritation and the depression which is so characteristic of the jaundiced state.

Fig. 1. Normal ducts.

Fig. 2. Long cystic duct.

Fig. 3. Cystic duct passing to ampulla.

Fig. 3a. Cystic duct passing to ampulla. Stone in common duct.

In April, 1943, she saw a doctor whose wife I had fortunately been able to relieve of similar symptoms due to congenital cystic dilatation of the common bile duct (Case 8) and he sent her to me. I found a deeply jaundiced and unhappy patient who in spite of her miseries showed a rare courage. She not only tried to joke and laugh at her troubles but still maintained the care of her personal appearance. It was the only occasion on which I was pleased to see a woman using lipstick and nail varnish. I explained to her that I might find that nothing could be done but advised operation. She willingly consented and the operation was performed at the London Hospital on April 28. There was much fibrosis but a short stump of the duct was found high up in the hilum of the liver. A long tube was inserted and the duct reconstructed with a flap of duodenum. In order to save time in her convalescence, instead of leaving the tube in her duodenum to be passed, it was turned up into the stomach and at the end of the operation was removed through a small incision in that viscus. The results were at first miraculous. The pain and jaundice disappeared at once. The stools were of a perfectly normal color and she again became bright and cheerful but alas, shortly after returning home, the symptoms all recurred and it was evident that with so much fibrosis the new duct had become constricted and the tube should have been kept in until the passage was firmly established. It was one of my hardest duties to have to tell her that yet another operation would be necessary. She again consented, and in July, I performed my usual reconstruction operation. A fistula formed for a few days but the jaundice disappeared and has not returned. At first she had some attacks of severe pain but these decreased. In October she was free from pain and jaundice and well except for an attack of Bacillus coli pyelitis.

It is too early yet to assess the final result but if she is now cured the result is mainly due to her unfailing courage and fortitude in refusing to become a drug addict and her faith in the power of surgery to aid her. If I have been the fortunate medium of her cure I have the great reward of having enjoyed the complete confidence of so brave a lady.

Such tragedies although becoming only too common today are of relatively recent occurrence. According to Mouat the first reconstruction was performed by Doyen in 1892, and von Stubenrauch had published the first paper proposing a fistuloenterostomy in 1906. It was only after 1905 when cholecystectomy began to replace cholecystostomy that attention was widely directed to the dangers of operation. Even in 1914 the report of a case was published by Sir Alfred Pearce Gould: in this case, for some unexplained reason, jaundice and a biliary fistula followed cholecystectomy and was cured by implanting the open cystic duct into the duodenum. It would seem evident that this was a case of an injured duct and what was thought to be the open end of the cystic duct was in reality the upper end of the divided common duct.

Since then the accident has become relatively common; even in 1920 Eisendrath was able to collect 51 reported cases and in 1937 Lahey had personally operated upon 35 patients. The frequency of the lesion is due to the fact that probably in no other part of the body is there so great a variation in the anatomy. In my own work with over 1400 operations upon the biliary tract including 940 cholecystectomies the variations have been so frequent that it becomes a very difficult matter to say what is normal. In my contributions to

Fig. 4. Double common duct (after Eisendrath).

Fig. 5. Looped cystic duct (after Eisendrath).

Fig. 6. Absent cystic duct.

Fig. 7. Double cystic artery.

this subject I have laid stress upon these variations and have shown how easy it is to injure the common duct and the arteries. Some very valuable anatomical studies of them have been published, perhaps the most important being those of Jacobson, Eliot, Eisendrath, and Wilson. So far, however, they are not described in the usual textbooks of anatomy and since failure to recognize them is one of the common causes of injury we shall consider them in brief.

Normal relationships. The position of the various structures generally regarded as normal and as usually depicted in the textbooks is that represented in Figure 1. The gall bladder is single, more or less fusiform in shape, and lies well to the right of the falciform ligament. The cystic duct arises on the inner side of the lower part of the gall bladder, the outer and lower pouch-like portion of which is usually known as Hartmann's pouch. It passes across to join the common hepatic duct while the cystic artery runs parallel to, and just deep to, the cystic duct. So great is the faith of many surgeons in the constancy of these relationships that even today the positions are often regarded as certain, and no steps are taken to verify them. In truth the variations are so frequent that many have come to regard the position just given as abnormal rather than normal. Abnormalities may occur in the shape and position of the gall bladder. It may even be double or absent or on the left of the falciform ligament, but these conditions do not enter into our present considerations.

Variations in the ducts. Not infrequently the cystic duct is much longer than just depicted and then runs downward to join the common duct either at an acute angle or even to run parallel with it (Figs. 2 and 3). In the latter case it may be bound to the hepatic duct so that both may be divided in the belief that only the cystic duct is present. Sometimes the cystic duct is so long that it joins the hepatic duct only at the ampulla. In this case a stone may lodge in the lower part and be entirely overlooked or it may pass up the common hepatic duct (Fig. 3a) and, since a probe or forceps may then pass freely into the duodenum, its presence may pass unrecognized. With so long a cystic duct a considerable portion may be left behind during a cholecystectomy and, if it contains a stone, may dilate to form a pouch as big as the original gall bladder, a condition I have described as reformation of the gall bladder. There have been two such cases in my series. According to Eisendrath there may be a double common duct or the cystic duct may form a spiral loop round the front or back of the common hepatic duct (Figs. 4 and 5). He also notes that accessory ducts may open direct from the liver into the gall bladder, and this I have found on a number of occasions a possibility which demands drainage in every case of cholecystectomy. Sometimes the cystic duct is much shorter than normal and very rarely is completely absent, the two hepatic ducts entering one side of the gall bladder and the common

Fig. 8. Looped right hepatic artery.

duct leaving on the other (Fig. 6). In such a case the duct is of necessity divided in removing the gall bladder. I have had 1 such case in my series (Case 2) which I have previously reported. Eisendrath gives a diagram which appears to represent a similar condition, also one of Lahey's cases was said to have no cystic duct at the first operation.

Variations in the vessels. These are extremely common. Most frequently there is more than one cystic artery. Eisendrath states that in his series there were 2 arteries in 12 per cent of the cases (Fig. 7). Every surgeon must be conversant with a second artery which lies anterior to the cystic duct. In such cases the accessory artery and sometimes, indeed, the only artery may arise low down. In Eisendrath's series it arose from the gastroduodenal artery in 17 per cent. If the surgeon is not conversant with this possibility an artery may be unexpectedly divided and, in an attempt to pick it up in a field obscured by a rush of blood, the ducts may be clamped or tied. A much more important variant is that the right hepatic artery may form a loop so that it lies immediately deep to the cystic duct in the position of the cystic artery (Fig. 8) and being mistaken for that structure is tied and divided. The right and left artery may anastomose freely in the liver substance when but little harm is done, but often there is no such anastomosis and then the right lobe of the liver will necrose and the patient die of hepatic insufficiency. Such cases have not come under my care for they die before a second opinion can be sought, but I am conversant with a few cases in which the accident has happened. Admiral Gordon Taylor, to whom abdominal surgery owes so much, informs me that he has known of several such accidents.

Pathological variations. A departure or an apparent departure from the expected anatomical arrangement may not always be due to a congenital variation but may arise from pathological processes. In many cases of cholecystitis, especially where there has been obstruction of the cystic duct, the gall bladder may become dilated and the inflamed Hartmann's pouch cover and become adherent to the cystic duct (Fig. 9). The common bile duct then appears to issue from the inner side of the pouch and is divided in the belief that it is the cystic duct. A very similar condition occurs if the pouch is still larger and is adherent to the common duct itself (Fig. 10). I have in many cases before the dissection is complete demonstrated this condition and have later been able to show, as the dissection has proceeded, that the first seen structure was the common and not the cystic duct. In spite of the frequency with which these and the congenital anomalies are present I am appalled to see the frequency with which surgeons, often of wide experience, are content to lift up Hartmann's pouch and with no dissection at all, often without even dividing the peritoneal covering, clamp and divide what they believe to be the cystic duct. It is not surprising, therefore, that the dreadful tragedy of injury of the common duct is becoming a relatively frequent accident. I have for long taught that in this area no structure whatever must be divided until all three ducts and the cystic artery have been clearly exposed and recognized.

Surgical accidents. Apart from difficulties due to abnormal relationships, injury especially to the common and hepatic ducts may accidentally occur when they are in their normal positions. Undoubtedly the most frequent cause of this is the failure to gain adequate exposure by careful dissection. Another common cause is that the gall bladder is pulled upon and if relatively mobile the common duct is drawn up in a loop so that its first part runs in line with the cystic duct and is divided in mistake for it (Fig. 11). This may happen when traction is applied to Hartmann's pouch

Fig. 9. Hartmann's pouch adherent to cystic duct.

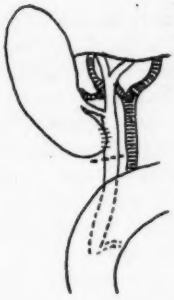

Fig. 10. Hartmann's pouch adherent to common duct.

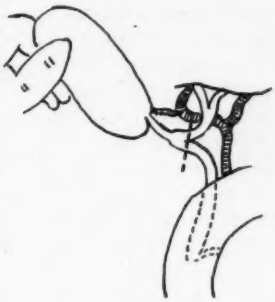

Fig. 11. Effect of tension on gall bladder.

Fig. 12. Common duct caught in artery forceps.

but is even more likely to occur with the older method of commencing the resection of the gall bladder from the fundus for then the parts are not only more mobile, but the field is obscured by blood escaping from the raw surface of the liver. I have been impressed by the fact that in so many of these cases the surgeon who performed the first operation has said to me "I do not think I could have divided the common duct for the operation was so easy." It is of course in the easy case that the tissues are dangerously mobile.

Eisendrath states that in his series 12 injuries occurred in this way. If the division takes place near the cystic duct a small portion only may be removed but if the common duct is divided low down the gall bladder is pulled upon further and what is thought to be an adhesion deep in has to be cut to free it. This is the common hepatic duct which is divided right up in the hilum of the liver. It is the most disastrous of all types of injury for the upper stump may be so short that it may be very difficult to find and suture. In some cases, indeed, it may retract right up into the hilum and at a second operation no trace of the proximal end of the duct can be found so that the lesion is almost certain to be fatal.

Another not uncommon accident is that the cystic artery, although recognized and isolated, is insecurely ligatured. The ligature slips and the depth of the wound is filled with blood. The cut end of the artery retracts either under or over the common duct and the artery forceps with which it is caught grasps the duct (Fig. 12), and either divides it or it is included in the fresh ligature. My experience agrees with that of Lahey who states that the description of the first operation so often emphasizes the fact that it was made difficult by much bleeding. There were 3 such cases in Eisendrath's series.

CLINICAL AND PATHOLOGICAL CONSIDERATIONS

Primary obstructions of the common bile duct may, of course, be due to many conditions other than injury, the most frequent being carcinoma, either in the head of the pancreas or in the bile ducts, calculus in the common duct, and chronic pancreatitis. The majority of these, however, do not come into our present consideration. Obstructions which arise after operation as well as persistent fistulas are undoubtedly, in the majority of cases, due to an injury of the duct. With this opinion Mayo and Wilson among others are in accord, but in a few cases the obstruction seems to be inflammatory in origin. Walters states that of 83 cases 17 were inflammatory. In such cases my own experience has been that the inflammatory change is a cholangitis perhaps associated with hepatitis, and that ulceration around a stone which has been given as a common cause of benign stricture is in fact rare. Mayo states that occasionally obstruction is due to fibrosis following gall-stone ulceration but if so the stone is usually in the stump of

the cystic duct. Sometimes the symptoms of obstruction appear so late after the operation that it is difficult to believe that they are due to an injury of the duct although it is quite possible that the injury was partial and was followed by a slow and progressive fibrosis ultimately causing complete stenosis. Such a sequence of events seems the more probable in that many of the operations performed for the relief of an injury have been immediately successful, but the symptoms have returned sometimes after a long interval and these relapses often appear to be due to progressive fibrosis. As far back as 1914 Mann reported a case in which obstructive symptoms commenced 5 months after cholecystectomy but an operation was required only at the end of 2 years. Wilson reported another in which obstruction only occurred 7 years after the operation and he quotes Judd as putting forward the view that these late obstructions are due to an obliterative cholangitis. Apart from these doubtful cases there are others in which it is definitely due to some cause other than injury at the first operation. The most important group are those due to the failure on the part of the surgeon to appreciate the nature of the pathological condition which consists of a double lesion. There may be gall stones associated with chronic pancreatitis or with carcinoma of the head of the pancreas. If the gall stones alone are recognized and the gall bladder is removed, obstructive jaundice will follow or if the common duct is drained there will be a persistent fistula. This is perhaps more likely to occur if the obstruction has led to hepatic failure with the presence of white bile, for the colorless fluid in the gall bladder may be regarded as the mucoid secretion behind an obstructed cystic duct. A similar error may be made with multiple carcinomas, one growth being low in the common duct and another in the cystic duct. Such errors would have been avoided if the surgeon had observed that the common duct was dilated or preferably had made sure that there was a free passage to the duodenum.

In this communication I am considering a series of 46 cases. The first group of 33 includes the injuries and 5 cases of congenital cystic dilatation of the common duct, for the majority of the latter presented as cases of jaundice following operation. The second group consists of 1 inflammatory stricture, 4 cases of chronic pancreatitis, and 8 out of my 49 cases of carcinoma of the common bile duct for they were all treated by reconstruction of the common bile duct.

Two syndromes may occur after an injury which has not been recognized at the time of operation. In the one the duct has been divided and after operation all the bile drains through the tube. The fistula persists, the stools become white, and it is manifest that there is external loss of all the bile. For a varying time the patient may remain in relatively good health but ultimately and sometimes rapidly goes downhill as a result of the complete loss of bile. In some of the reported cases, attempts have been made to reintroduce the bile into the stomach either as a drink, usually unsuccessfully disguised, or through a stomach tube. In the other group of cases in which the duct has been tied or has gradually stenosed, there is the immediate or slow onset of obstructive jaundice, the color of the patient slowly changing from bright orange through dull green to gray until in the end he comes to look more like a half caste than a jaundiced patient. Throughout the stools are clay colored and contain no trace of bile. The skin shows excoriations from the intolerable itching. There is rapid loss of weight and soon the onset of an extreme mental irritability. The liver function fails so that at a later operation the dilated upper duct contains a thin white fluid like water with often no trace of bile. As a rule the deterioration is much more rapid than in the first variety, but some unfortunate sufferers become confirmed morphine addicts, for severe colic-like pain may occur with the obstruction, and may survive even for several years (see Case 45). At a second operation the first type is generally the better operative risk but the upper end of the duct is small and surgical manipulations are difficult. In the second type the proximal duct is dilated and therefore the operation is easier but the patient is a much worse risk. In some patients the symptoms are combined. There may be a fistula but the duct is narrowed so that obstructive jaundice is also present. Many

of the patients have had several operations in an attempt to overcome their disabilities.

At operation the field is greatly obstructed by dense adhesions, the omentum, the colon, and the stomach being firmly united to the abdominal wall, and the duodenum, omentum, or stomach being densely adherent to the original bed of the gall bladder. There is no type of operation which more clearly exemplifies the rule that no attention whatever must be paid to the pathological condition until the anatomy has been restored. By gentle dissection with the edge of the knife, used more like a paint brush, at the line of junction all these adhesions can be gradually separated by a completely bloodless procedure. The structures are gradually recognized and retracted until the region of the edge of the gastrohepatic omentum is reached with the liver above and the duodenum below. Somewhere in the mass is the divided duct. Usually its distended upper end or the opening of the fistula may be seen. The former may be difficult to distinguish from the portal vein. In such cases much time may be saved by aspirating the doubtful swelling with a fine hypodermic needle as first advised by Balfour. In nearly all my own cases the lower end of the duct could be discovered only with great difficulty or could not be found at all. Mann and Jackson appear to have had a similar experience. In the worst type of case often where there have been two or three previous attempts at repair, the hepatic artery and portal vein may be exposed in their whole length and no trace of the duct can be found. A hypodermic needle should then be inserted into the hilum, and in fortunate cases may strike the dilated duct up in the substance of the liver. All these operations are prolonged and difficult, the patients are bad risks, and the mortality is of necessity high.

OVERLOOKED AND FATAL CASES

It is probable that there have been a considerable number of cases in which an opening has been made into the common duct, it has not been noticed, there has been a free escape of bile into the peritoneal cavity, and the patient dies within a few days. No postmortem may be held, but in any case no report is made.

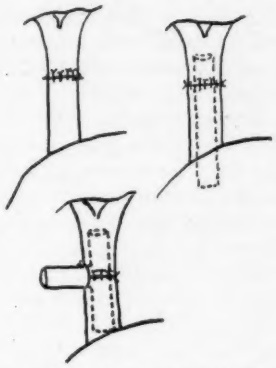

Fig. 13. Methods of end-to-end suture.

The frequency of such an accident is impossible to determine. However, it was the occurrence of an accident of this sort in my practice more than 30 years ago which first directed my attention to injury of the common duct. I operated upon a woman of 52, performing cholecystectomy for acute cholecystitis. She rapidly developed peritonitis and on the 4th day a pelvic drain was inserted and bile and pus escaped. She died next day. At the postmortem 1 inch of the common duct was found to be missing. Fortunately the specimen has been kept and the missing piece of common duct was found attached to the cystic duct. It taught me a most valuable lesson but, unfortunately, gained at the expense of a life. I am pleased to say that I have never accidentally injured a common duct since and hope that what knowledge I have gained on the subject may save others from a like experience.

METHODS OF REPAIR

End-to-end suture. As a rule end-to-end suture is applicable only at the time of the first operation when there is no fibrosis and the lower end of the duct has not become shrunken. It can therefore be used if the injury is recognized at once. In some cases a direct suture is used, in others the repair is made around a rubber tube passed either down to the ampulla or through into the duodenum. Recently the use of a vitallium tube has been advised by Pearse (Fig. 13). Mayo advises end-to-end suture around a T tube wherever possible. It is also advocated by Eliott, Ginsburg and Speese and

Eisendrath. It may also sometimes be used where there is a small localized stricture either fibrous or carcinomatous which can be excised and yet leave enough healthy duct above and below for easy approximation. In my own series end-to-end union was possible in only 3 cases. In the case of congenital absence of the cystic duct, union was accomplished over two tubes inserted into the hepatic ducts. In 2 cases fibrous strictures, one of which was probably due to injury, were excised and simple end-to-end suture without tube was performed. The one following injury died 3 days after operation. These operations like every other method are always difficult. Even with an immediate union the duct may be small and deeply situated so that much time is consumed and the patient's reserves are strained. Of the patients who recover, the end-results are not always satisfactory. In my own case of absent cystic duct, the patient made a good immediate recovery but after 3 years had recurrent attacks of pain, rigors, and jaundice. Further operation was refused, she gradually developed enlargement of the liver and spleen and 11 years after operation died from a severe hematemesis due to portal obstruction. Eliot and Eisendrath report similar recurrences. The third patient made a good recovery and was well at the end of 3 years.

Dilatation of the stricture. It is only in a few cases that such a form of treatment is possible and it is but seldom that it is likely to be successful. Of the few cases reported in the literature it is only noted as having been attempted previous to some more radical step being undertaken. It will be noted that in 3 of my own cases a second or third operation had been unsuccessfully performed to dilate the stricture before they came to me. In 2 of my own cases in which there was only a slight narrowing following a previous operation, dilatation alone was attempted; both had recurrent attacks which were slight, however, and the patients were able to lead a normal life.

Local plastic operations. In certain cases local operations have been performed on the narrowed part of the duct. In most cases these have consisted of a longitudinal incision of the narrowed area which is then sutured transversely either by direct suture or around a tube. It is not likely to be successful unless the stricture is very narrow. Eliot states that it is only likely to be temporary and Walters reports 3 cases in which the results were only fair, there being attacks of incomplete obstruction since the operation. Lahey has reported 3 cases sutured around a T tube, in all of which good progress was made and patients were well, respectively 9, 10, and 14 months later. In 2 of my cases (17 and 32), this operation had been previously attempted; in 1 case with no, and in the other with only temporary, relief. It is a method I have never used.

Choledochoduodenostomy. This is a long accepted and perhaps the oldest method of overcoming an irremovable obstruction of the lower part of the common bile duct where the gall bladder, either because of its previous removal, or because of its diseased state, is not available for the performance of a cholecystgastrostomy or duodenostomy. It was apparently first performed by Reidel in 1881 but the patient died of biliary leakage. The first successful case appears to be that of Sprengel in 1891. Later cases were reported by Swain and Fullerton, in some of which the anastomosis was carried out with a Murphy button, but Rowlands advocated the use of a simple suture in 1907. It soon became popular and Sasse even advocated its use in cases of obstruction by a calculus. Hörz performed the anastomosis around a rubber tube which was brought out through a second opening in the duodenum lower down and was drained externally. It is an unsatisfactory method, however, in the class of case under consideration because the ordinary method of lateral anastomosis necessitates a dilated duct in close approximation to the duodenum, and it is therefore usually replaced by one of the methods of direct or indirect implantation. Walters states that the best results follow choledochoduodenostomy or hepaticoduodenostomy but it is not clear whether he means a lateral or a terminal anastomosis. In my own 5 cases of congenital cystic dilatation of the common duct which often closely resembled cases of injury, in that colic and jaundice followed a previous operation, sometimes even a cholecystectomy, it was the method of choice. I have also used it in a large number of cases

Fig. 14. Fistuloenterostomy.

Fig. 15. Direct implantation (Mayo method).

Fig. 16. Omental reconstruction round tube (Sullivan method).

of carcinoma of the lower duct and head of the pancreas and in cases of chronic pancreatitis, but I have never considered it as suitable for the treatment of cases of injury.

The use of autogenous grafts. If there is a long gap between the cut or dilated end of the duct and the duodenum, it is perhaps natural to consider the transplantation of a free graft to bridge the deficiency. In 1913 Molineus advocated the use of the appendix for this purpose, and in 1914 Giordano and Stropeni used portions of a vein. Davis and Lewis in 1913 experimentally used strips of fascia. It never seems to have become a popular method although Ginsburg and Speese reported a case, successful after 2 operations, in which a portion of new duct was made from a strip of posterior rectus sheath. I have never used it, as it seemed to me that a free graft deprived of its blood supply would be very prone to necrose, and its use, therefore, be followed by an immediate fistula or by a later obstruction.

Fistuloenterostomy. In 1906 von Stubenrauch proposed that the external end of a permanent biliary fistula should be dissected free and anastomosed with the intestinal tract (Fig. 14). It was apparently first performed by Sutton in 1910, but without success, a fecal fistula following. According to Walters the first successful operation was accomplished by Williams of Boston in 1914, the patient being alive and well in 1929. Just as with a pancreatic fistula it is an attractive measure, for a portion of the fistula can easily be dissected out with very little disturbance to the patient, the prolonged dissection to lay bare the duct being avoided. Walters advocates its use and reports 4 cases of his own and quotes cases by St. John and Lilienthal. Lahey has also reported 2 successful cases. Theoretically, however, there are objections to its use. It is a common experience to find that long continued fistulas tend to close for a time, the patient then becomes jaundiced, and later the fistula breaks down again. If this happened after the anastomosis the condition would be as bad as before. There are also the dangers that the fistula may necrose and, since the opening is not valvular, that sepsis may ascend from the intestine and cause cholangitis. Hoag believes that these objections are not only theoretical, for he says that although at least a dozen successful cases have been reported there have been more failures than successes. Lahey also finds it unsatisfactory, stating that of 14 cases only 2 had permanent relief. Wilson also brings forward strong arguments against its use. He quotes Eliot as having collected 41 cases of which 22 were united to the duodenum, 18 to the stomach, and 1 to the jejunum. There were 18 deaths and 9 developed strictures, one a second time. Most of the failures were due to contraction of the tract. I have not used it nor had it been previously attempted in any of my cases. If no duct can be found, the only hope is to form a fistulous tract from a puncture in the liver and later anastomose it to the intestinal tract.

Direct implantation. The direct anastomosis of the cut or obstructed end of the duct to the intestinal tract would seem to be the natural method, but a simple anastomosis would have the theoretical objection that there would be no valve, and ascending sepsis with cholangitis

would be likely to occur. The first operation seems to have been performed by W. J. Mayo in 1905, but with his customary genius he made the opening into the duodenum semilunar in shape so that a valve was formed (Fig. 15), the patient being alive and well after 15 years. It has since remained the most popular of all methods and should be employed where possible. Balfour states that in overlooked cases it is the best method and that in no case was there evidence of subsequent obstruction. Walters, however, in a later communication says that of 6 cases the results were very good in 5 but 1 developed cholangitis. Many surgeons support its use though several have modified it, especially by the use of a tube in forming the anastomosis. The case previously quoted of Sir Alfred Pearce Gould and reported in 1914 was treated by simple anastomosis with apparent cure. Packard, in 1908, and Harrington, in 1909, reported successful cases treated by the Mayo technique. Mann used a tube sutured into the duct and then invaginated into the duodenum after the manner of a Senn-Kader gastrostomy. Jacobson employed a similar method but used a loop of jejunum brought up in front of the colon as the duodenum was not mobile.

The end of the duct should preferably be implanted into the duodenum but if the latter is too fixed or does not appear to be healthy the stomach or a loop of jejunum may be used but, as Wiedemann pointed out, the colon should never be utilized as the risk of ascending infection is increased. If a tube be used Wilson advocates that it should not pass far into the duodenum or it may come away too quickly. McArthur, on the other hand, advises it, as it will pass more easily. This question will be discussed more fully later. In my own series, there were 6 cases all due to previous injury. In each case the divided end was implanted into a crescentic opening in the duodenum by the Mayo method. In 4 cases in which the duct was not greatly dilated a tube was used and made to project well into the duodenum. In 2 a simple anastomosis was performed. Two of the patients did not survive operation. In 1 of these the duct was greatly dilated with white bile. There is no doubt that this is an evidence of hepatic failure and the patient is a bad operative risk, the sudden lowering of pressure within the duct being of considerable danger. In such cases Ravdin and Frazier have made the valuable suggestion that as a first stage a tube should be fixed into the stump of the duct, brought out through the wound, clamped, and the liver slowly decompressed, the anastomosis being completed at a second operation. Of the 4 cases that survived, 1 died 8 years later with cholangitis, 2 were alive 2 and 3 years later, but 1 was having some attacks of pain and jaundice. The last case has been watched only 7 months. His was a bad case; he had had 3 previous operations. He has had some attacks since operation but they are getting less.

Reconstruction of the common bile duct. In many cases there is so much dense fibrosis and the proximal end of the duct is so short that direct implantation into the duodenum is difficult or impossible. A loop of jejunum might be drawn up but at such a height there is a risk that it might become angulated and therefore some form of indirect implantation or reconstruction of the duct is often preferable. Many different methods have been used, but in nearly all the new duct is formed around a rubber tube. According to Mouat this was first carried out by Doyen in 1892 but the patient died on the 9th day from hepatic insufficiency. Interest was first generally stimulated by the work of Sullivan who in 1909 operated on dogs, bridging a gap in the duct with a rubber tube. Around the tube, omentum was wrapped and sutured in place (Fig. 16) and when the tube was passed this formed the new duct. Soon after Brewer reported 2 cases, 1 very successful, and 1 in which the patient died soon after, apparently from obstruction. Brandt also reported 5 successful cases, but Wilms found that in his first 3 cases the tubes gave rise to much trouble by escaping into the peritoneal cavity. Two of the 3 tubes which replaced the first ones were vomited. Hagler in 1918, reporting a case of his own in which patient died 7 months later with cholangitis, states that up to that time 22 cases repaired by Sullivan's method had been reported. Theoretically the method suffers from the drawbacks that leakage is likely to occur round the flap which will then be prone to give way.

Even if this does not occur the new tube is not lined by epithelium and is thus at best only a fistula which will tend to contract. The opening into the duodenum is in no way valvular and thus ascending cholangitis would be probable. In support of these objections Wilson says that of 38 collected cases there was a mortality of 39 per cent, and that recurrences were common with cholangitis, abscesses of the liver, and biliary and duodenal fistulas.

A consideration of these difficulties led me to devise the operation published in 1915 whereby a new duct having a valvular opening was fashioned from a flap of duodenum sutured around a tube. This method can be used as a terminal reconstruction when the duct is completely divided, or as a lateral reconstruction through a side opening made into the dilated duct. This was suitable for some cases of carcinoma extending far up the duct.

The steps of the operation are as follows: By careful dissection the upper end of the duct is freed and opened if necessary. The duodenum is drawn up and sutured to the posterior edge of the duct. A wide flap is then cut from the whole thickness of the anterior wall of the duodenum and turned downward. The upper end of the resulting opening in the duodenum is closed with a few stitches. A piece of rubber tube, of as large diameter as possible, is inserted into the duct and sutured in position with catgut. The lower end is passed into the lower part of the duodenal opening. The duodenal flap is then turned up and sutured round the tube to the duodenum and to the anterior margin of the cut duct (Fig. 17). Schrager and Hoag both have devised methods of making a new duct out of a tube of gastric mucous membrane, but in neither case is the opening valvular. Ginsburg advocated a modification of my method whereby the flap was turned up instead of down, and R. P. Sullivan reported a case he had treated by this method using a T tube. Seven months later there was a recurrence. I tried this modification in 2 cases, but found it more difficult, and it has the drawback that the opening is not valvular.

In my own series there have been 16 cases of terminal reconstruction, 1 for fistula following cholecystectomy and obstruction from chronic pancreatitis, one after excision of carcinoma of the duct, and 14 for injury. The patient with chronic pancreatitis made an immediate recovery, was able to fight in Gallipoli in the last war, and was free of all symptoms when last heard of 15 years after operation. The patient with carcinoma did not survive the operation. The 14 cases of repair after injury were all difficult. Several had had a second or even a third operation. The operative field was obliterated by dense adhesions which required prolonged and careful dissection to restore the anatomy. The remaining portion of the duct was of varying length sometimes being high up in the hilum, at other times being an inch or more in length. Contrary to Mayo's observations, often no trace of the lower end of the duct could be found. On many occasions Balfour's device of proving a doubtful stump by aspirating through a hypodermic needle was of great value and saved much prolonged dissection. The majority of the patients were bad risks and especially was this the case when the duct was filled with white bile. Three of them did not survive operation, usually dying with evidence of hepatic insufficiency, 4 are quite well and have remained so after intervals of 10, 6, 2 years, and 4 months, respectively. Two have since died of other conditions, 1 of meningitis 3½ years later and the other of carcinoma of the colon 2 years later. Three died 3, 2, and 1 year later with cholangitis and 2 had a recurrence.

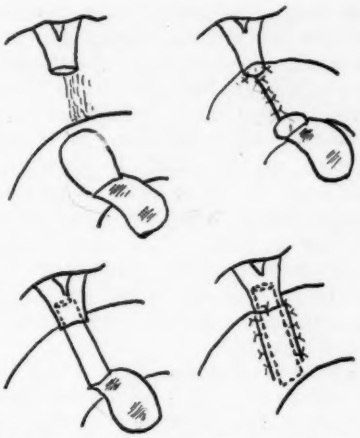

Fig. 17. Reconstruction by duodenal flap.

There were 11 cases of lateral reconstruction, 3 from obstruction from chronic pancreatitis, 7 with carcinoma of the duct and pancreas in whom a simple choledochoduodenostomy did not seem suitable, and 1 with a fibrous stricture. Of the 3 with chronic pancreatitis 2 did not survive, the other was in perfect health 6 years later. Of the 7 cases of carcinoma 3 did not survive but the others gained considerable relief up to periods of 1 year. The patient with fibrous stricture, although 76 years old at the time of operation, was in perfect health and leading an active life traveling at the end of 5 years.

Hepaticoduodenostomy. There are certain cases, probably those in which the duct was divided after traction upon it so that the upper division was at the hilum, in which no trace of a duct can be found. The cut upper end may have retracted up into the liver and be entirely lost. Even in such cases a hypodermic needle should always be inserted in the hope that the stump of a dilated duct is just beneath the surface. If none can be found the condition is almost hopeless although attempts have been made to establish an anastomosis between the ducts in the liver and the intestinal tract.

Eliot has collected several cases of this type, the first being that of Garré in 1908 and another of Doberer in 1910 both of which he says were successful. In 1936 he had collected 11 cases, all German. In these cases the liver was punctured with a cautery and drained. If thereby a biliary fistula is formed it is later anastomosed to the duodenum or jejunum but, as Wilson points out, the drainage can be only partial so that a biliary fistula may not relieve the jaundice and strictures of the fistula are likely to follow. In 1912 Lameris cut the free edge of the liver and sutured it to the intestine. Infection spread to the ducts, and the patient died 8 months later. There were 10 small ducts opening into the intestine. In 3 of my own cases in which no duct could be found as also in 1 case of congenital obliteration of the bile ducts, a puncture was made and a tube was sutured into it. In 1 there was a very slight escape of bile for 2 months which then ceased. In the 2 others, no bile at all escaped and the patients, although still alive for 9 and 10 months, respectively, after operation, were living in profound misery and steadily going downhill.

The use of rubber tubes. It will have been noticed that in many of the operations tubes, generally of rubber, have been used. In immediate end-to-end unions their function has been mainly that of an internal splint to facilitate the introduction of the suture. In this case, generally speaking, the smaller the duct the more useful the tube, the larger ducts being more suitable for direct suture or implantation. In old standing cases with much fibrosis or absence of a portion of the duct, there has been more uncertainty as to their value. If a tube is used it may, as mentioned in cases of Sullivan's operation, escape into the peritoneal cavity, and Wilson states also that it may be displaced upward or may become kinked. Many surgeons have feared that being a foreign body it would, if long retained, set up a cholangitis or would become encrusted with bile salts and its lumen thereby be occluded. In one of my cases (Case 28) the tube was retained for 6 months and did so become occluded, but in all other cases it was passed much earlier.

In many of the cases which are reported, it is stated that the tube has not been noted to have been passed, but apparently no trouble arose. Today, if there is any doubt, its presence would be determined by the x-ray. On the other hand if no tube be used, any gap which is not lined by mucosa is almost certain to contract and even if a mucosal lining be obtained throughout, dense external fibrosis may cause much constriction, ultimately progressing to complete obstruction and it would seem to be necessary to retain a tube until the new passage is established. There is, however, a difference of opinion as to the time required for this. Wilson says that a tube should not pass into the duodenum if it is required to stay in place for a long while. McArthur states that if a long tube be used reaching down into the duodenum it will pass easily and evidently regards this as desirable. Many surgeons have attempted to overcome this difficulty by using T tubes which can be left *in situ* for a long time and withdrawn when it is thought that the new passage is established. In 2 of Lahey's

cases it was left in for 4 months and in R. P. Sullivan's case for 6 months. There are, however, grave theoretical drawbacks to the use of T tubes. Their withdrawal is very prone to injure the duct, and for this reason I never employ them in biliary surgery. The formation of a lateral opening is also very undesirable as it may originate a biliary fistula. Recognizing these difficulties Eisendrath and Hörz both devised operations in which the tube was passed down the duodenum, brought out lower down, and drained externally. It could be withdrawn when desired. In my reconstruction method the tube always passes into the duodenum and has been extruded spontaneously, in all but the case mentioned above, in periods varying from 10 to 42 days. In Case 30 it was brought out through the stomach in the manner of a gastrostomy tube, and removed in 2 weeks, but the patient died in 2 years with cholangitis, and in Case 33 it was merely used as a splint and removed through the stomach at the end of the operation. Obstruction recurred in 3 weeks. In the future I shall always leave the tube projecting into the duodenum to be passed naturally for I believe it should remain in place for several weeks. If obstruction should recur while the tube is still in place, as confirmed by the roentgenograms, then it could be removed through a small incision made in the duodenum.

The subject of surgery is very vast and I have only opened for discussion one very small section which might well have been entitled "How to remove the gall bladder." An equally wide discussion might be devoted to the question of "When to remove the gall bladder." The conclusions I have put before you are based on 30 years of major abdominal surgery. Hippocrates has said that experience is fallacious and judgment is difficult but if, as the result of my experience, I have been able to impress upon you, and especially upon the younger members among you, one great principle of surgery, that no structure in the human body must ever be divided until it and its immediate surroundings have been clearly displayed, then my 30 years' work has not been wasted.

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DEEP QUIET VENOUS THROMBOSIS IN THE LOWER LIMB

Preferred Levels for Interruption of Veins; Iliac Sector or Ligation

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IN a recent communication (14), an account was given of quiet venous thrombosis (phlebothrombosis) in the legs as a cause of pulmonary embolism in ambulatory persons, showing how unsuspected processes of this sort might account for a variety of thoracic symptoms simulating cardiac and pulmonary disorders. In discussing the nature of deep venous thrombosis beginning below the knee, attention was called to the various courses which such a disease might pursue: (1) It might heal without ever progressing upward above the knee or causing pulmonary embolism; (2) it might develop into a femoro-iliac thrombosis (phlegmasia alba dolens) in which case it was very unlikely to cause pulmonary embolism; or (3) it might form a soft propagating thrombus, seriously threatening pulmonary embolism.

It is desirable to consider in greater detail these various developments; for the more accurately one can distinguish between the courses taken by a lower-leg, deep, venous thrombosis, the more successfully can one make use of surgical section[1] of the principal vein of the limb, not only in forestalling, or putting a stop to, pulmonary embolism, but in securing for the patient the least subsequent disorder of the venous return. On the whole, the tendency at the moment is to make higher, that is, more proximal, interruptions than originally were used. In this communication, then, the reasons for dividing the principal vein at one level or another will be pointed out and the pros and cons of the iliac and even vena caval divisions will be discussed. There will, of course, be included the thromboses which arise under all sorts of circumstances—those which occur as a result of trauma, operation, childbirth, and the serious diseases which confine patients to bed, as well as the less common ones of active life.

One must get away from the old notion that thrombosis in the lower limbs usually starts in the upper femoral and lower iliac veins. It was formerly supposed that the sort which causes the familiar phlegmasia alba dolens usually takes origin from a deposit of platelets due to the eddies and cross currents in this region, and very little attention was paid to processes starting in the foot and leg. It is true, of course, that venous thrombosis does sometimes begin in the region of the groin and even in the veins within the pelvis, but, today, owing especially to the work of Bauer (3, 4), Frykholm, Roessle, and others and to more careful observations by pathologists and clinicians as well, it is realized that thrombosis in the deep veins of the legs not only starts as a rule below the knee but that such a process may, in its development, give rise either to nonobstructive masses in the femoral and iliac vessels, that is, phlebothrombosis, or to the completely obstructive inflammatory condition known as thrombophlebitis. Thus while one must distinguish between a quiet, nonobstructive, embolus-threatening disease and an inflammatory obstructive one, one should realize that both sorts may well have a common source.[2] As yet it is difficult to say what proportion of lower-leg thromboses take one course or another, though it is probable that of all those which begin in the deep vessels of the calf, less that half finally will so fill the femoral and iliac veins as to bring on the full-fledged obstruction of phlegmasia alba dolens. The others may remain confined to the lower leg, or give rise to fatal pulmonary embolism, or produce states of incomplete venous obstruction with or without embolism.

[1] In this communication, only operative treatment is considered. The use of such anticoagulants as heparin and dicoumarol is not discussed. In the earlier communication already mentioned, treatment by anticoagulants alone was not advised. They have, however, been used by the writer occasionally in support of vein division. He believes that combinations of dicoumarol and heparin hold out considerable promise, especially if heparin, in a satisfactory medium, can be administered intramuscularly once or twice a day, so that prolonged and continuous action is secured. Such methods require, of course, the most careful frequent examinations of the blood.

[2] Welch and Faxon go even farther and indicate that the distinction between the quiet process, Ochsner and DeBakey's "phlebothrombosis," and an outspoken thrombophlebitis is of little clinical importance.

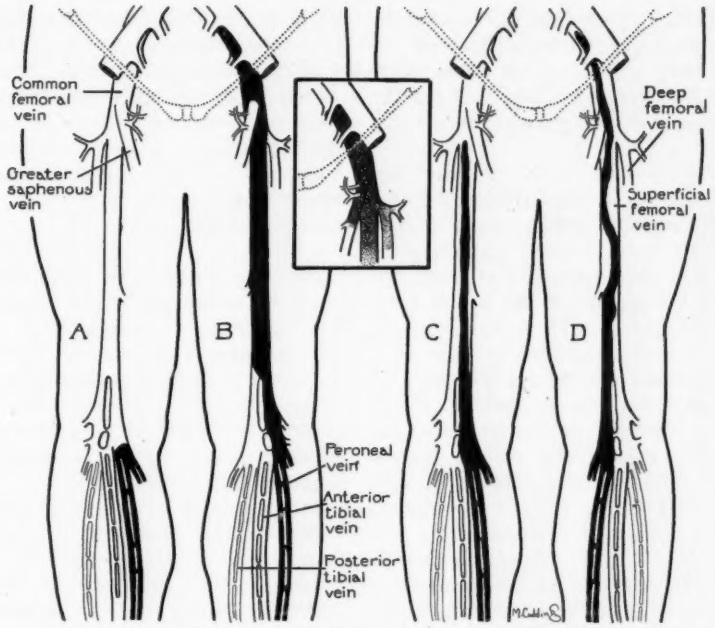

Fig. 1. Diagrammatic sketches, showing various courses which a deep, lower-leg, quiet thrombosis (phlebothrombosis) may follow. In each case, the disease is shown as starting in one of the three main venous systems of the calf. A, The quiet thrombosis is represented as having failed to progress above the popliteal region. There is no propagating mass in the popliteal or femoral vein. B, The quiet thrombosis has progressed into the femoral vein where it now fully obstructs the femoral and external iliac veins, and is represented as ending cleanly at the junction of the common iliac and hypogastric veins—a present day conception of femoroiliac thrombosis or phlegmasis alba dolens. No attempt is made to indicate the inflammatory reaction about the great vessels or the involvement of collateral channels. (The insert represents an older conception of femoroiliac thrombophlebitis, starting in the region of the groin and spreading distally for an indefinite distance into the superficial femoral vein). C, The thrombosis has formed a propagating floating mass, not adherent to or obstructing the femoral vein. Its proximal end might or might not be seen on opening the superficial femoral at the groin. At this stage a fatal pulmonary embolism is seriously threatened. D, The thrombosis has reached a fairly advanced stage, being adherent to, without obstructing, the femoral vein and having extended through the left external into the common iliac vein. At this stage, emboli of fair size may readily be detached.

The accompanying diagrammatic sketches will give some idea of these various courses which can briefly be described as follows:

1. The initial thrombosis in the lower leg develops into a thrombophlebitis and causes the typical swelling of phlegmasia alba dolens (Fig. 1, B)

2. The initial thrombosis remains confined to the veins of the lower leg in which it originates and there heals (Fig. 1, A).

3. The initial thrombosis propagates through the popliteal into the femoral vein and forms a soft floating mass capable of causing pulmonary embolism on a large or small scale (Fig. 1, C).

4. The initial thrombosis propagates through the popliteal into the femoral vein where it becomes more or less adherent, without causing obstruction, and may come to occupy most of the femoral, and external iliac, advancing at times into the common iliac vein and even into the vena cava (Figs. 1, D and 2, B).

It is proposed to deal in detail with the non-obstructive, embolus-threatening processes

but, before doing so, to describe briefly the obstructive, femoroiliac thrombophlebitis, explaining why this form does not seem to require surgical intervention and recounting the sorts of treatment which seem most acceptable today.

Femoroiliac thrombosis—its source and treatment. There are at least three good reasons for believing that this process usually arises from deep, quiet, lower-leg thrombosis. First, Bauer (3, 4) has traced, by venographic studies, the development of the full-fledged, obstructive phlegmasia alba dolens from its source in the deep veins below the knee. Second, one can sometimes secure a history of pulmonary infarction, indicating that a soft, nonobstructive thrombosis has preceded by some weeks the appearance of the typical edema and discomfort of a femoroiliac thrombophlebitis. And third, there are observations, such as are related by Conner, in experiences with typhoid fever, of very suggestive early signs in the form of pain and tenderness in the toes, feet, and calves before the unmistakable swelling of "phlebitis" becomes apparent. Bauer (4) and others have estimated that 90 per cent of femoroiliac thrombophlebitis is of such origin and that only 10 per cent, perhaps, commences in the groin or pelvis. The exact ratio between the two varieties is really not important. It is enough to realize that, in the light of today's knowledge, only recognition and operative treatment of its *early*, pre-obstructive stage can prevent the full development of the disease.

The essential difference between phlegmasia alba dolens and an advanced quiet thrombosis (phlebothrombosis) lies in the as yet unexplained inflammatory reaction about the great artery and vein in the femoral and iliac regions. For only when the venous stream is fully obstructed by a solid thrombus does this reaction set in, giving rise to the edematous limb, enlarged from toes to groin, often painful and usually marked by tenderness over the femoral vessels, together with some perivascular inflammatory thickening at the groin. The reaction may be minimal or may take the form of an acute, nonsuppurative exudate involving the nearby nervous and lymphatic structures quite as much about the artery (11) as the (15) vein. It certainly offers an explanation of the occasional vicious local spasmodic constriction of the artery and of the irritating impulses which appear to travel centrally from the region involved, calling forth reflexly, by way of the sympathetic system, the peripheral vasoconstrictions which are recognized today as a major cause[1] of the edema and discomfort in phlegmasia alba dolens.

The treatment of thrombophlebitis is directed toward releasing the generalized vasoconstriction by making a sympathetic block with procaine—repeatedly if necessary, as Leriche and Kunlin (16) and Ochsner and DeBakey (18) have pointed out. The matter is brought up here only to indicate that the prevention of embolism is not a problem. Indeed, there is a very good general rule, almost a law, that the greater the swelling and discomfort, the less the danger that a soft, detachable mass exists. And if, in the presence of phlegmasia alba dolens, embolism actually occurs, one can be reasonably certain that it comes, not from the vein of the swollen limb but from the other, or innocent appearing leg. In all probability, exploration and division of an inflamed, fully obstructed vein, with extraction of such of its adherent thrombus as can be sucked out, will relax the associated vascular constrictions, but this is substituting a rather considerable operation for a lumbar sympathetic block. Nor is it clear at what level such a division should, if at all, be performed. If an operation is undertaken, its advantages and disadvantages should be understood much more fully than is at present the case. And whether or not sympathetic procaine block is used, the swollen leg of thrombophlebitis should be drained of its fluid by elevating the foot of the patient's bed and by allowing such motion in bed as can comfortably be made. As fever disappears and the swelling recedes, exercise of the dependent leg should gradually be instituted. Bandaging from toes to knee is necessary at

[1] One should recognize that venous obstruction is, by itself an amply sufficient cause for edema, as Zimmerman and deTakats have shown experimentally. And the lymphatics, if involved in the inflammatory reaction, or even perhaps if they are not, may be unable to carry off the large amounts of increasingly proteinized tissue fluid due to serious venous obstructions. In any one instance, one can only guess at the relative importance of these various factors, but, supposedly, the greater the discomfort (or pain) edema and generalized cyanosis (without obvious engorgement of the veins) the more likely is a reflex vasoconstriction of the arterioles and venules to be the principal factor responsible for edema.

this time, when the venous blood is finding new channels of egress from the limb. Edwards and Edwards have pointed out that even though canalization of the principal vein subsequently occurs, the valves of the thrombosed vessel are necessarily ruined, making it functionally useless.

HEALING OF THE INITIAL THROMBOSIS WITHOUT EXTENSION OR EMBOLISM

How often this takes place in the absence of operative treatment, or indeed of any treatment at all, is impossible to say. Very little help is to be obtained from statistics.[1] In a recent study, based on adequate diagnostic criteria, Welch and Faxon (22) in 1941 find that the ratio of fatal embolism to recognizable "phlebitis" in 250 cases at the Massachusetts General Hospital during the period 1935–1939 was 1 in 25 and that 1 patient in 3 with "phlebitis" suffered an infarct. Such figures relate, however, to all stages of thrombosis, early and late, and entirely to hospital experience, which appears to vary from institution to institution. Most surgeons hold that neither healing nor freedom from embolism can be predicted, and that once a diagnosis of deep venous thrombosis in one or both legs is reasonably certain, whether the chances against a fatal embolism are 15 to 1, 25 to 1, or even higher, they are not justified in withholding a safe, easily performed interruption of the femoral vein. They expect, in fact, to operate on many patients in order to save the life of one—a perfectly justifiable attitude. Actually, as will presently appear, there is no way of telling whether a deep lower leg thrombosis has ceased to extend or is forming a soft propagating thrombus which will wave in, without in the least obstructing, the femoral vein (Figure 1, C).

The clinical evidence of a deep, quiet, venous thrombosis in the calf is obviously quite different in ambulatory persons and in those already confined to bed. No age beyond infancy is free from the accident of thrombosis, though it is most common in the 6th decade and beyond. When attacked in active life, the individual may notice some degree of lameness of the calf in walking, some little edema of the ankle; occasionally, only such vague symptoms as hardly to trouble a busy person. There may have been a minor accident or unaccustomed strain. Any lameness and swelling which are present will be relieved by a few days' rest in bed but will recur on renewed use of the limb.

When thrombosis occurs during posttraumatic, postoperative or postpartum life in bed, or in the course of any serious illness, there may be even less to call attention to the local

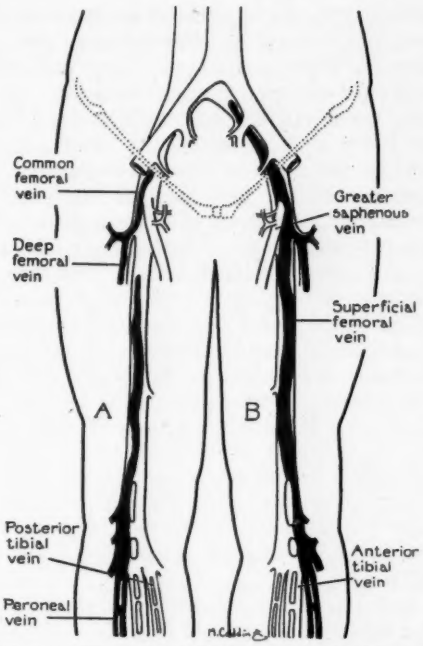

Fig. 2. Diagrammatic sketches of advanced stages of a quiet, lower-leg thrombosis. A, A propagating thrombus has advanced into the upper right femoral vein, and at the same time an independent thrombosis has started in the deep femoral (profunda femoris) propagating into the common femoral vein. Section of the superficial femoral vein would neither reveal or control this second process. B, A propagating thrombus has become adherent to, without obstructing, the left femoral vein and has advanced into the common iliac vein. Its proximal end may easily be detached. An associated thrombosis is present in the deep femoral system.

[1] The interesting statistics of Barker, Nygaard, Walters and Priestley (1940–1941) give no information as to this question, since the criteria for a diagnosis of deep, lower leg thrombosis are not stated. However, they make the important point that once an embolism has occurred the chance that a fatal embolism will follow is approximately 1 in 5. To show how unsatisfactory the diagnosis of venous thrombosis had been during the decade previous to 1940, in only 25 per cent of all cases of pulmonary embolism covering a 13 year period at the Mayo Clinic was a clinical or pathological diagnosis of thrombophlebitis made. These figures relate solely to postoperative experience.

disease. It is under these circumstances that embolism is so apt to come out of a clear sky. However, there is often pain in the calf, ranging from mere soreness to a real ache. There may or may not be some swelling of the ankle and lower leg. There may be tenderness of some of the toes, of the foot or of the calf. More especially, there may be some sign of irritability of the great posterior calf muscles. This can be brought out by strongly dorsiflexing the foot—dorsiflexion sign. The muscles may merely resist passive dorsiflexion, which will be less complete than upon the opposite side, or there may be discomfort, referred to the back of the calf or the popliteal space. The muscles, to the grasp of the fingers, will often feel full and a little tense. Finally, if the individual can sit or stand up, the foot of the dependent leg will perhaps appear faintly cyanotic, again as compared with the opposite side. It may be necessary to leave the legs dependent for several minutes to bring out this sign.

If conservative treatment is elected, the idea behind it is that thrombosis will usually cease to progress when and where it meets the active current of another vein. There is an opportunity for this favorable event in the coming together of the several systems of veins of the lower leg in the popliteal region. One should expect it most often in the young and vigorous and least often in the elderly and feeble. The patient should be allowed freedom of movement in a bed of which the foot is elevated from 4 to 6 inches. Ten days will usually see all signs of thrombosis disappear. Then the leg is exercised actively, at first in elevation and finally, then bandaged, in actual walking. Such treatment has previously been described. Originally, the writer's (12, 13) attitude was that only if, after a fair trial of conservative measures, the signs and symptoms of thrombosis recurred, should femoral section be urged. However, since experience has shown that nonoperative treatment is more often followed by recurrence than by a permanent cure, and since embolism is always a threat, an early femoral interruption should prevail over conservatism. The level of section or ligation, in the absence of any signs of a propagating thrombus in the femoral, should be the superficial femoral vein at the groin, just below the great branch entering from the thigh (profunda femoris). This procedure will briefly be reviewed under the next heading, that is, thrombosis in the lower leg complicated by a propagating thrombus in the femoral vein.

THE PROPAGATION OF A DEEP THROMBOSIS IN THE CALF INTO THE FEMORAL VEIN IN THE FORM OF A NONOBSTRUCTIVE, NONADHERENT THROMBUS

This is the state with which surgery chiefly deals. It represents an early stage of the progress of thrombosis into the femoral vein, the dangerous stage before the thrombus becomes in any degree adherent. It is the source of the long pulmonary embolus which kills so quickly. However, a small fragment of the propagating mass often breaks off—a preliminary shot, as it were, causing signs of moderate pulmonary embolism in the form of substernal pain, pleuritic pain or even merely cough, faintness or breathlessness. Perhaps, least often, the embolism excites the classic pain in the side associated with hemoptysis. Reference to pulmonary embolism is made here to indicate that it offers the most certain evidence of the presence of a loose, propagating thrombus. Without it, one can only make a diagnosis, by the signs described under the previous heading, of a quiet deep thrombosis below the knee. For the unattached propagating mass adds nothing to the local picture produced by that condition.

In this connection, Allen, Linton, and Donaldson (1943) make the following statement, based on their most recent experiences at the Massachusetts General Hospital:

> "During 1942, many vein interruptions were undertaken upon patients with symptoms localized to the lower leg, and in this group thrombosis of the femoral vein is not expected. Our present opinion is that, if possible, the operation should be carried out before thrombosis has extended into the femoral and iliac veins. As our diagnostic acumen improves in detecting early thrombosis, the number of negative explorations will increase, yet the protection afforded by the operation is not diminished."

Their table of diagnostic signs indicates that 81 per cent of their patients showed something significant on their chart, 67 per cent

showed some degree of swelling of the limb, 61 per cent showed some evidence of tenderness; and in 41 per cent, the initial symptom was some sort of thoracic pain. They stress the advantage of noting on the chart an elevation of temperature, pulse and respiration, and they deprecate the value of what DeBakey, Schroeder and Ochsner have properly insisted on calling phlebography rather than venography. They find, contrary to the views of these writers and to the earlier conclusions of Welch, Faxon, and McGahey (23), that positive clinical evidence of thrombosis with a negative phlebogram has been secured in one-third of their cases studied. And they believe that since the ideal time to section the femoral vein is when thrombosis is still localized in the lower leg, it is in early cases, when phlebography is most difficult to interpret that a positive result obtained by this means is most desirable. In fact, they take issue with those who advocate phlebography as a prime factor in the early diagnosis of phlebothrombosis.

The operative treatment of a deep, lower leg thrombosis, whether a loose, propagating thrombus is merely suspected of being, or is known to be, present, consists in exploration and division of the femoral vein at the groin. Ordinarily, in the early case, the superficial femoral vein, below the entrance of the profunda, is exposed, isolated between guy ligatures or rubber tubes, and opened. The direction of the incision is not vital, though a long cut parallel to and about 2 centimeters below the inguinal ligament is perhaps most satisfactory. For by this route the great saphenous vein, which is the quickest guide to the femoral, is most easily found. The femoral vein itself lies mesial to the artery, often almost directly behind it. The profunda enters somewhat distal to the saphenous, as is shown in the various diagrammatic sketches.

As a rule, either no thrombus is seen in the vein or a nonadherent, floating mass is encountered. In the former case, the vein is merely sectioned between double ligatures; in the latter, the head of the table is elevated to favor a backward flow of blood, and the soft clot is sucked out through the smooth glass tube. Then the vein is doubly ligated above and below the opening, and divided. The circumstances under which the common femoral, proximal to the deep femoral (profunda femoris) should be closed will presently be discussed. Under the conditions outlined here, one need hardly fear the presence of thrombosis above the deep femoral or entering the main vein from it, as is shown in Figures 1, D and 2, A and B. However, for full assurance, many surgeons prefer section of the common femoral to interruption of the superficial femoral vein distal to the profunda branch. In any case, one need not feel obliged to divide the opposite femoral vein, a procedure required chiefly when bilateral signs are present and sometimes when no signs are discoverable in either leg to account for serious or repeated pulmonary embolism.

THE PROPAGATION OF A PARTLY ADHERENT, NONOBSTRUCTIVE THROMBOSIS INTO THE FEMORAL VEIN, THE EXTERNAL ILIAC VEIN AND HIGHER

This advanced stage may properly be called a subacute or even chronic form of quiet thrombosis. Though it approaches an obstructive thrombophlebitis, it differs in several important respects. For edema is never a serious feature, and embolism is rather common, often recurrent. In other words, since blood continues to flow past the thrombus, soft masses of clot which are likely to be present at the proximal end of the process and may be detached at longer or shorter intervals. If of large caliber and in considerable gross quantity, these masses are capable of plugging the pulmonary vessels with fatal effect. But in some instances, repeated small embolism, even over a considerable period, seems to do comparatively little harm.

An unpredictable feature of the high, incompletely obstructive thrombosis is involvement of the deep branch of the femoral vein. When an adherent thrombus occupies the main channel, one should take it for granted that the profunda also is partly filled with soft clot. Whether this is an independent process or has arisen from the primary disease is difficult to say. Frykholm indicates that thrombosis may be not only independent but primary here. Fine, Frank, and Starr give an account of a fatal case of this sort, not sub-

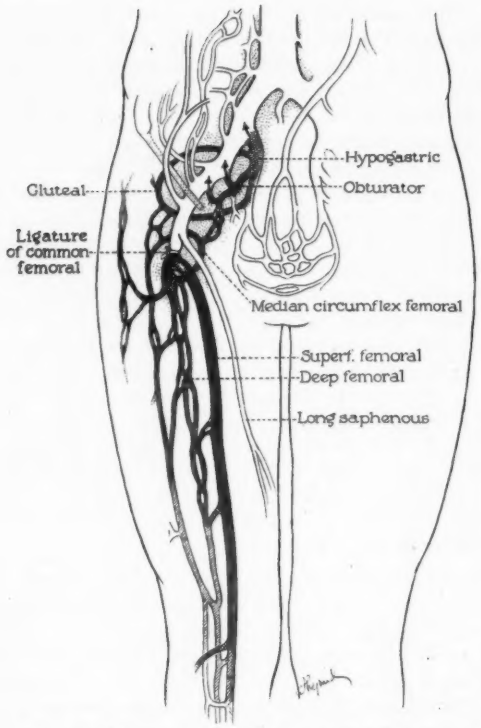

Fig. 3. A diagrammatic sketch showing the nature of the venous return from the right leg and the collateral circulation when the common femoral vein is interrupted.

jected to operation. In any event, one is justified in assuming that in an advanced disease, especially one of several weeks' duration, even though adherent thrombus is not found on the opening of the superficial femoral vein, a dangerous thrombosis may still be present in the profunda, ready to propagate into the common femoral, an important consideration in treatment, as will presently appear.

A rather characteristic sign of the advanced type of thrombosis is cyanosis. This varies in depth, depending upon the degree to which the disease has penetrated the veins which ordinarily would offer collateral pathways, especially in the thigh. For the thrombus in the main femoral and iliac veins, though by no means completely obstructive, so permeates these vessels as to cause considerable venous congestion in the corresponding limb. And if many collateral outlets are involved, the limb must become in some degree cyanotic. This cyanosis is not necessarily evident when the patient lies in bed but becomes noticeable as the leg is made dependent. One can often make a diagnosis of an incompletely obstructive femoroiliac thrombosis by letting the patient stand up for a minute or two, whereupon the skin, from the knee down, will take on some degree of blueness. Edema, especially in a patient already confined to bed, is strongly suggestive of such a process. If present, it is usually confined to the ankle and lower leg.

With such signs in evidence, certain others may or may not be discovered. There may be some slight thickening about the femoral vessels at the groin, making the arterial pulsation at that point less distinct to the examining fingers than that of the opposite side, and in chronic cases, well advanced toward full obstruction, a tendency to a spasmodic type of constriction of the femoral artery may very rarely be noticed.

A fairly frequent complication of the extensive process is thrombosis of some of the superficial veins. Usually, a superficial thrombus, in either a varicose or an apparently normal vein, is an independent affair, having little tendency to invade the deep vessels. But it may be secondary to a deep thrombosis. Thus when a superficial thrombus is noticed in the greater or lesser saphenous system, and there is any reason whatever to suspect the presence of a deep process, the superficial thrombosis is evidence for that process rather than against it. Barker, Nygaard, Walters, and Priestley indicate that among 51 cases of postoperative, fatal pulmonary embolism in which the location of the venous thrombosis was clinically recognized, it was found in the lesser saphenous vein on 30 occasions as compared with 18 in the femoral and iliac veins. They reason from this very common involvement of the lesser saphenous, that since detachment of an embolus of any size from so small a vein is exceedingly unlikely, "the fatal embolus was probably a detached, newly formed thrombus from the femoral or iliac vein which had not existed long enough to produce clinical signs or symptoms." Perhaps a better way to put the matter is to say that the superficial throm-

bosis was probably secondary to a deep process in the calf, from which propagation of soft clot into the femoral vein had also occurred.

As a background for the appearances which suggest an advanced disease, there may or may not be present the familiar restriction of full dorsiflexion of the foot. Usually, the posterior calf muscles will in some degree be irritable, but a positive diagnosis can be made in the absence of a dorsiflexion sign or full, tense calf muscles. In this connection, it would be of great advantage if some corresponding signs were available to indicate thrombosis in the veins among the great muscles of the thigh. Actually, no such signs have as yet been discovered. One can only infer that in the presence of a process of several weeks' duration and especially when cyanosis in the lower leg is detectable, thrombosis in the profunda femoris is very likely to be present.

How high the advanced, partly adherent but still nonobstructive thrombosis may have gone, is usually difficult to say. It seems to progress farther on the left than on the right. Usually, there is no thrombus of importance above the external iliac vein, an important consideration especially in common iliac and vena caval interruptions. Repeated embolism, over a period of weeks, months, or years, may properly be considered evidence of a high process, from the proximal end of which fragments of moderate size are easily broken off.

When an earlier thrombosis or thrombophlebitis, followed by canalization and destruction of all valves in the femoral vein, is known to have occurred, the situation and progress of a recurrent thrombosis is particularly unpredictable. The venous return is already being cared for by collateral veins. Even an extensive process in the old, canalized channel need cause no signs, yet embolism may take place, repeatedly in some instances. The recurrent thrombosis will usually have begun as usual in the calf where typical signs may perhaps be discovered. But whether or not such signs are present, one should be prepared to find that the region from which embolism has occurred is high, at or above the groin, wherever, in fact, the vein has previously suffered disease. Embolism recurring over a period of years is especially apt to originate in such a vessel.

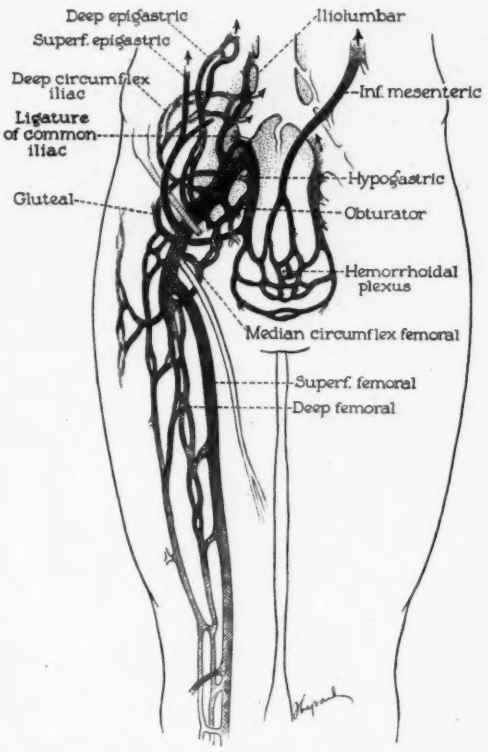

Fig. 4. A diagrammatic sketch as in Figure 3, showing the very much more abundant collateral venous return when the common iliac vein is interrupted.

To sum up, the diagnosis of an advanced, nonobstructive, adherent thrombosis which has come to occupy the femoral system and perhaps some part of the iliac veins, rests first, in ambulatory patients, on its chronicity. In these, local signs of thrombosis or episodes of pulmonary embolism will have been noticed on and off, for weeks or months. In posttraumatic, postoperative, and postpartum cases, and in thrombosis complicating any serious illness, cardiac or other, an advanced stage may be reached with far less warning and, so far as can be ascertained from observation of the local signs, in a relatively short time—a period of days or weeks. The suggestion that thrombosis has reached the groin or

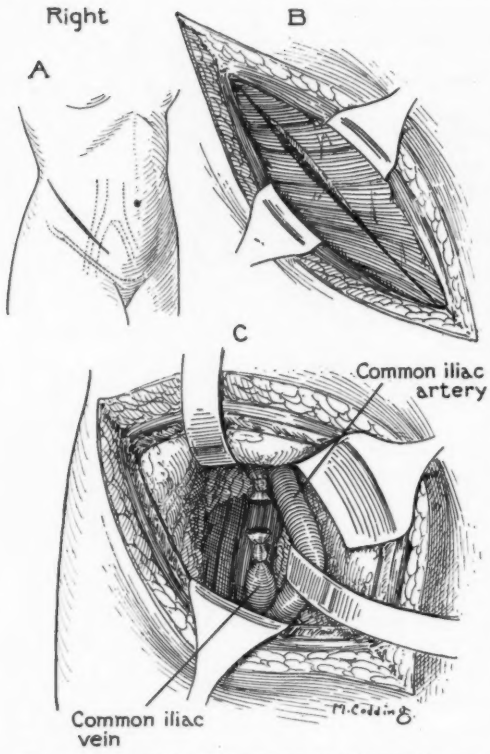

Fig. 5. A, B, and C, The extraperitoneal operative approach to the right common iliac vein, showing that the vein lies lateral to the artery which hardly requires the degree of retraction used. In C, the vein has been doubly ligated with silk (including a stitch above and below) and divided. A little more retraction, upward and mesially, would expose the vena cava.

higher is most likely to come from the presence of those signs of an advanced process which have already been described. Slight cyanosis of the foot and lower leg, evident as a rule only when the leg is dependent but sometimes detectable in the horizontal position, offers strong support. Persistent or recurrent edema of the ankle is helpful. Tenderness over the femoral vessels and superficial complicating thromboses are confirmatory. Phlebography may be of great assistance, by demonstrating an irregular caliber and loss of valves in the femoral vein. On the other hand, if a picture is had even of only a few inches of normal femoral vein, one can be sure that no thrombosis has ascended from the lower leg.

Treatment is always operative, the real problem being the level at which the principal vein of the limb shall be interrupted. When the partly adherent thrombosis, past which blood is freely flowing, is discovered in the upper femoral vein upon exploration at the groin, the custom of most clinics has been to suck the soft thrombus out through a smooth glass tube as large as can be inserted into the common femoral vein, and if, while the head of the table is raised and the flow from below is controlled by a guy ligature or rubber tube, a good back-flow of blood is then secured from above, the common femoral is sectioned between ligatures. This section cuts off any possible subsequent thrombosis which may enter from the profunda femoris but does not guarantee that a thrombus will not re-form in the external iliac vein or higher. It has been argued by those who advocate this procedure as a routine that even if thrombosis should recur at a higher level, emboli of large size are seldom cast off and a fatal embolism is very unlikely indeed. In any case, interruption should not be made in the superficial femoral *distal* to the profunda branch, for serious if not fatal pulmonary embolism can surely occur from a propagating thrombus entering the common femoral from this vessel.

Evidence will now be presented that the situation just described should, if possible, be avoided. That is, an advanced nonobstructive thrombosis, requiring extraction of a soft, partly adherent clot, should not be attacked in the upper femoral vein but rather at a higher level. This will require a refinement of diagnosis not always attainable. The matter is discussed below.

INTERRUPTION OF THE COMMON ILIAC VEIN

Though interruption of the common femoral vein, as already explained, offers a considerable degree of protection against subsequent serious pulmonary embolism, it cannot give the assurance of a yet higher division, for example, in the common iliac vein. But there is another reason why section of the common femoral vein, under the conditions just outlined, is undesirable. This is the unsatisfactory collateral circulation which follows upon such a division. The blood from the now fully

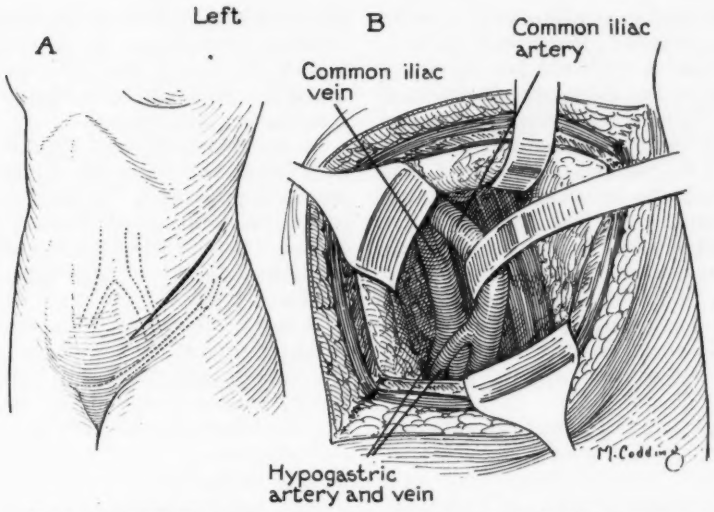

Fig. 6. A and B, The extraperitoneal operative approach to the left common and external iliac veins. The vein lies mesial to the artery and at a deeper level. The artery may require even more retraction than is shown in the sketch. The exposure of the vein is more difficult than on the right.

obstructed femoral system must find a passage through partly obstructed collaterals into the veins of the pelvis, abdominal wall, buttocks and so on, by way of small and not particularly numerous channels. Whereas if the common iliac vein is divided, blood can escape via the common femoral through the deep epigastric, the deep circumflex iliac, and particularly through the hypogastric vein. By way of this last channel, it may pass through rectal vessels into the inferior mesenteric vein or to the opposite side of the pelvis, and, in women, an additional collateral field is offered by the uterine and ovarian veins. The difference in the collateral pathways offered by interruption at these two levels is shown in Figures 3 and 4, which speak for themselves. Backing up these anatomic considerations, clinical experience indicates that while serious venous congestion and swelling sometimes follow interruption of the common femoral vein when the superficial and deep femoral systems are partly filled with adherent thrombus, section or ligation of the common iliac vein seems to leave no such troubles behind. As a result of an experience now covering 14 such interruptions, these conclusions seem justified.

The question of the greater difficulty in performing the higher operation now comes up. First, as regards the anesthesia. It will probably be agreed that division of the superficial or common femoral vein can very easily be performed under procaine infiltration. The same is hardly true of the common iliac operation. The ideal approach is, of course, the extraperitoneal one, very much like exposure of the ureter at the pelvic brim. The incision commences above in the flank and is carried down parallel to the inguinal ligament nearly as low as the inguinal canal. For this, a nerve block with novocain is perfectly adequate, but, unfortunately, after the peritoneum has been pushed mesially, and retraction is made to clear the iliac vessels, there is a drag on the intestinal mesentery which is decidedly painful. This pain quiets down while retraction is steady, but it is certainly a disagreeable feature of the procedure. Thus a local anesthetic is not easy to use, especially for an operator not accustomed to it. Spinal anesthesia will probably be preferred, an added risk, perhaps, in patients having cardiac disease and especially high blood pressure. Very likely, also, this anesthesia increases the danger of pulmo-

nary embolism on the operating table, due, as O'Neil has suggested, to the possible detachment of an embolus while the patient's back and thighs are flexed during the insertion of the spinal needle. For such reasons, a general anesthetic will usually be required.

The second increased hazard of the high interruption is due to disturbance of the retroperitoneal lymphatics. One sometimes notices, in operations for thrombosis, hypertrophied lymph nodes which lie upon and about the vessels of the pelvic brim. Should these be receiving infectious material, the manipulations required for ligation or division of the vein will perhaps contaminate the retroperitoneal space.

A third risk lies in the danger of separating, from the common iliac artery and from the tissues behind it, the great vein, which, especially in the case of an old thrombophlebitis, is often very easily torn. The same is, in some degree, true of the femoral under similar conditions, but the femoral vein is far more accessible and easily handled. One is conscious, especially in freeing the left common iliac (Fig. 6)—it lies median to, and deeper than, the artery, not lateral to it, as on the right—that if it were torn, hemorrhage would be serious and difficult to control. Moreover, if one is actually to divide the vein, and particularly if one is to look for a contained thrombus, one must free it for some distance, so that it can be opened between guy ligatures and then ligated by double ties above and below, of which the ones next the cut ends shall be transfixing stitches. Such an operation, of course, consumes time and effort, and increases the risk of tearing the vein. One is tempted, therefore, to ligate without dividing, a procedure offering no view of the vein's contents and less likely than division to obstruct it permanently. Possibly also, failure to divide the vein encourages the persistances of such vasoconstriction as may be present in the venous tree of the limb.

All these disadvantages, of which the risk of tearing the vein is the most serious, seem to be outweighed by the finality with which the higher interruption, of the common iliac especially, obstructs the vein *above* the usual source of embolism, including processes in the profunda femoris, and by the excellence of the collateral circulation. Until one becomes accustomed to it, one can hardly believe that an operation, seemingly so radical, leaves so little venous congestion behind.

As between division of the common and of the external iliac vein, the former operation is obviously preferable. This is in great part due to the availability of the hypogastric vein as a collateral when the common, rather than the external, iliac vein is interrupted. But the common is actually the more accessible. On both sides, the external iliac vein lies mesial to the artery and at a deeper level. It is always somewhat difficult to isolate. Even on the left, where the common, as well as the external iliac vein lies mesial to the artery, the common, owing to the nature of the extraperitoneal approach, is the more readily exposed. And on the right side, the difference is even more marked. For the right common iliac vein, *lateral* to the artery and easily separated from it, is remarkably accessible (Fig. 5). It is reasonably so in the obese patient.

Examples of common iliac section and ligation have previously been published (14). The operation has been used when a reasonably certain diagnosis of thrombosis of a non-obstructive sort, rising as high as, or higher than, the inguinal ligament, has been made. In many instances, embolism had already occurred. In others, it had seemed to be threatened. In yet others, there had been several attacks of thrombosis without embolism and the attempt to prevent further recurrence seemed indicated.

As yet, little information has been secured in these high interruptions as to the proximal extent of the thrombosis. In the 6 right iliac sections, the vein was explored 5 times and in no case was thrombus encountered in the common iliac. In the 8 left sided operations, the vein was usually ligated without opening it. On one occasion, it was explored without finding a thrombus. On 5 others, the vein appeared to be the scene of an old thrombosis which had left its wall discolored and, to the operator's mind, friable. In each case a fresh thrombus was believed but not proved to be present. Full exposure and exploration, with retraction upon guy ligatures, was thought to

carry too great a risk of tearing the vessel. Simple ligation in continuity, even though made about a possible soft thrombus, seemed the safer procedure. In the 2 other cases, a seemingly normal vein was ligated without exploration. Nevertheless, the impression has been gained that thrombosis is far more likely to advance above the external iliac vein on the left than the right. Whether the attempt to suck out soft thrombus through the opened vein is worth the added risk which the procedure entails is debatable. Probably, on the very rare occasions when much pulmonary embolism has already occurred, the attempt will be desirable, in order to guard against further immediate detachment,[1] but these are also the occasions demanding the very simplest, shortest, and most bloodless operation. Further experience is needed to settle this problem.

INTERRUPTION OF THE VENA CAVA

This operation is probably indicated in the presence of bilateral thrombosis which is believed to have risen in the main venous stem, on both sides, to or about the level of the inguinal ligaments. It is certainly to be preferred to separate ligation of each common iliac vein, and is decidedly less radical than it sounds. For it really offers very little more obstruction to the venous return from either leg than division of the common iliac vein on the corresponding side. Actually, there are no, or only very small, lateral branches between the point at which a common iliac is ordinarily divided and the point, a few centimeters proximal, at which the vena cava itself is interrupted. Its only disadvantage, so far as the return circulation from each leg is concerned, is that it prevents the shunting of blood from one side of the pelvis to the other across the midline—a matter relatively easy when only one common iliac vein is shut off.

As yet, experience is insufficient to determine the state of the venous return from the legs after occlusion of the lower vena cava when a fairly extensive thrombosis is present in both legs. Some information, however, is available as to the state of the circulation when vena caval ligation has been used for septic thrombosis in the uterine and ovarian veins. Collins, Jones, and Nelson indicate, in a preliminary report, that, following such ligation, the venous pressure in the legs is raised only for a short time, for it falls rapidly in the first weeks after operation. Indeed, the problem involved has been whether or not the operation successfully ends the escape of septic material and emboli from the pelvis rather than whether or not vena caval interruption is compatable with a satisfactory venous return from the lower limbs. Certainly occlusion of the vena cava must cause far more venous congestion when performed for an advanced venous thrombosis in both legs than for even an extensive process in the veins within the pelvis. In all cases, the operation should be used only by those familiar with the isolation and ligation of large vessels. It is not yet indicated as a routine when the situation and source of embolism are unknown.

Technically, the procedure is not at all difficult. The vena cava lies to the right of the aorta in the lower lumbar region, and the incision used for exposing the right common iliac vein, extraperitoneally, offers an entirely adequate exposure. It is only necessary to sweep back the peritoneum a little farther toward the midline and slightly higher in order to obtain access to the vena cava. As in the case of the iliac veins themselves, the vena cava may be fixed rather firmly at some one point, though much of its circumference is easily exposed. It may be not only difficult but dangerous to clear enough of it to pass rubber tubes or guy ligatures about it, incise it and suck out thrombus, but it should not be difficult to pass a curved smooth clamp around it, being careful to hug the surface of the vertebrae posteriorly, and one or two ligatures of good sized braided silk should offer a satisfactory interruption.

It must be understood that this extraperitoneal procedure is only appropriate to cut off

[1] Since this paper was prepared, a case report, (21) dealing with this very matter, has come to hand. A soldier, 28 years of age, on active service and relieved from duty because of fever and thoracic signs, was found to have suffered from two attacks of pulmonary embolism, the source being an advanced thrombosis which had caused minimal signs in the left leg. At operation, tubing was passed about the lower vena cava and both common iliac veins. Soft thrombus projecting from the left common iliac into the vena cava was extracted, and the common iliac vein sectioned close to the vena cava. After one more small embolism, the soldier recovered and suffered very little subsequent edema of the limb. Undoubtedly, more venous thrombosis and embolism occurs in young men of the military services, whether or not injured or wounded, than is generally supposed.

thrombotic processes arising from the legs. In case of embolism from a thrombosis which is believed to be established in the uterine and ovarian veins, it must necessarily be insufficient, for in that case the ovarian veins also require division. Under such circumstances, a transperitoneal approach must be made, preferably a midline incision beginning somewhat above the umbilicus and giving sufficient room to expose both the vena cava and the ovarian veins.

CONCLUSIONS

1. Thrombosis of a quiet type (phlebothrombosis) commencing in the deep veins below the knee, is the source of most nonobstructive processes threatening pulmonary embolism as well as most obstructive inflammatory ones responsible for painful swelling of the whole lower limb (thrombophlebitis).

2. Thrombophlebitis of the fully obstructive type presents no satisfactory indication for operations, but rather for release of the associated vasoconstriction by lumbar sympathetic block.

3. It is desirable and usually possible to distinguish an early stage of quiet, deep venous thrombosis, when the process is still confined to the lower leg or has given rise to an unattached propagating thrombus in the popliteal and femoral veins, threatening pulmonary embolism. The signs of such a state are discussed and the clear indication for femoral interruption, to forestall or stop embolism and prevent the development of phlegmasia alba dolens, is pointed out.

4. An advanced stage of quiet, deep venous thrombosis, more or less adherent but not obstructive, can also be distinguished. Its signs are discussed. Thrombosis will often have propagated above the inguinal ligament into the external and, occasionally, especially on the left, the common iliac vein. With such a process, thrombosis of the deep veins among the muscles of the thigh (profunda femoris system) is usually associated. Thrombosis in these deep veins may even be present when no thrombus is found on exploration of the superficial femoral vein below the profunda.

5. The advantages of interruption of the common iliac vein for all such advanced, quiet, venous thromboses, are discussed, and the operative procedure, for both the right and left limbs, is described.

6. Some observations upon interruption of the vena cava are made.

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CANAVALIN, A NEW ENZYMATIC BACTERICIDAL AGENT

Preliminary Report

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As a result of the author's previous work a new enzymatic bactericidal agent called canavalin has been discovered. The present paper gives the method of its preparation, experimental data showing its *in vitro* action, and certain preliminary information as to its clinical use in patients.

Experimental work leading to the product canavalin has been carried out by me for about 10 years. The sequence of progress was as follows: First it was noted that the blood serum of animals, including man, contained a variable amount of a substance which inhibited hemolysis of red blood cells. It became apparent that the quantity of this substance in the blood could be increased by giving thiamin chloride. After considerable effort methods were successfully devised for isolating this substance from blood serum, for making the substance *in vitro*, and for isolating it from this last named source.

At this time the function of the substance was obscure. Its physical characteristics were those of a co-enzyme (4, 5, 6, 7). With this experimental lead various enzymes were investigated in an attempt to find the enzyme with which this unknown co-enzyme functioned. Eventually it became obvious that the substance acted as a co-enzyme against polysaccharides (starch, glycogen, etc.) when an extract of jack bean meal was a part of the reacting mixture.

At this point in the search it was recalled that Avery and his co-workers (1, 2, 3) found that certain substances of bacteria, particularly bacteria of the pneumococcus group and the Friedlaender's group, are of a polysaccharide nature. When emulsions of living bacteria were substituted by me for starch as substrates, oxidation occurred as readily as with starch or glycogen as shown by an oxygen uptake from the air in the closed system of a modified Warburg instrument and the development of substances in the liquid contents of the reacting chamber which reduced Benedict's and Fehling's solutions. Culture of the residual mixture showed the bacteria to be dead (Figs. 1 and 2). This enzymatic action against bacteria was considered extraordinary because the enzymatic action occurred against living organisms. It is well known, of course, that dead bacteria are susceptible as substrates to enzymatic action. It was also considered extraordinary that oxidation occurred from oxygen of ordinary air. It is the author's belief that this bactericidal action of canavalin results from an oxidation of polysaccharides in bacteria and that the oxidation of these substances destroys the life of the organisms. Emulsions of the colon bacilli, pneumococci, Friedlaender's bacilli and staphylococci were used as substrates with similar oxygen uptake. Cultures of the bacterial emulsions mentioned were sterile. When oxygen was substituted for air in the closed system there was some increase in the speed of the reaction, but the difference from that obtained with atmospheric oxygen was not striking. When nitrogen was substituted there was no reaction.

The immediate thought was that, since the enzyme system reacted in an artificial mechanical arrangement to kill bacteria, perhaps it might be of value in the treatment of infectious disease; that it might also destroy bacteria infecting the body. The results of clinical use of the material are summarized later in this paper.

Canavalin is a mixture of an enzyme and a co-enzyme solution, separately extracted and mixed. The enzyme portion is an extract of jack bean (canavalia ensiformis—8). It also has been extracted by me from soy beans, liver, and white potatoes. The jack bean is the best source. The co-enzyme portion of canavalin is associated with the vitamins of the water soluble B group. Thiamin and ribo-

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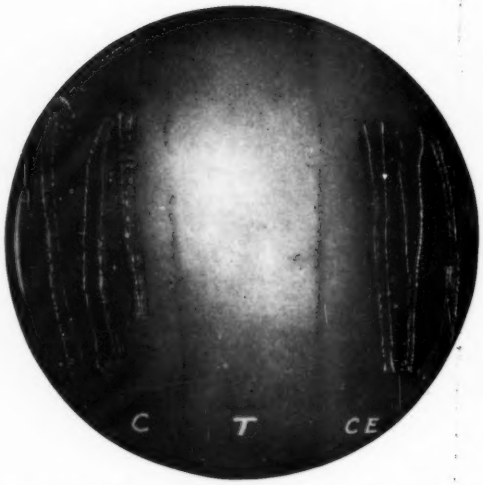

Fig. 1. *T*, Subculture of colon bacillus after treatment with canavalin; *C*, control, same as *T* but untreated by canavalin; *C.E.*, control, original culture of colon bacillus.

flavin are used to produce *in vitro* a supply of co-enzyme. This co-enzyme is called by me "vitatropin" and has the physical characteristics usually possessed by a co-enzyme—thermostability, filterability, and the property of being precipitated from a watery solution by an organic solvent. It is an interesting fact that both enzyme and co-enzyme have been found by me to be present in normal blood. Quantitative tests for content of both these substances in the blood have been devised.

The oxidative canavalin reaction with bacteria as a substrate takes place with equal ease when the medium contains milk or blood as when the medium is a watery solution. The hypothetic importance of this is that the blood has been shown to contain catalase-like substances which inhibit enzyme reaction. It can be assumed, therefore, that the oxidative reaction in question is not inhibited by the catalase-like substance in the blood. Members of both gram-negative and gram-positive groups of bacteria are oxidized by canavalin, although gram-positive seem to be more susceptible to its action (Fig. 3).

Action of the enzyme portion of canavalin does not take place unless the co-enzyme is present. Since the co-enzyme (vitatropin) is normally present in blood serum, the enzyme will always give some reaction in the presence of blood and a suitable substrate.

The apparatus used for determining enzyme action is a modified Warburg apparatus. This enables one to measure in millimeters positive and negative pressure in a glass capillary "U" tube which is connected to a closed system where the enzymatic action occurs. Mechanical controls provide constant temperature and agitation. Brodie's solution is used in the apparatus as the labile liquid.

PREPARATION OF CANAVALIN

Soy bean or jack bean flour is extracted by a mixture of water and an organic solvent, such as alcohol. A clear supernatant fluid is separated by centrifugation, precipitated by acetone, and the supernatant fluid again recovered by centrifugation. A solution of a heavy metal salt is added to this supernatant fluid. The enzyme forms, hypothetically, a heavy metal enzyme combination. The metallic portion of the combination is removed in the usual way, as an insoluble precipitate, leaving the enzyme in solution. To this enzyme solution is added a solution of vitatropin (co-enzyme). The co-enzyme portion has been previously discussed by me as "inhibitory substance and OBT." It has now been given the name vitatropin. Vitatropin is extracted from a mixture of a cellular tissue and thiamin chloride which has been allowed to stand for a week with frequent shaking and daily heating for 1 hour at 70 degrees C. After this time it is absorbed on insoluble barium sulfate and eluted with a weak ammonia solution, from which it is crystallized. The method of preparation of vitatropin is entirely empirical. Canavalin is prepared by mixing the enzyme and co-enzyme solutions. The optimum proportions of enzyme solution to co-enzyme solution is as yet not determined.

IN VITRO STUDIES OF CANAVALIN

An action curve of a given batch of canavalin was plotted (Fig. 4). The points determined were four. The abscissae represent amounts of canavalin solution in cubic millimeters as transposed to linear measurements, the ordinates the height of negative pressure in cubic millimeters of Brodie's solution (trans-

Fig. 2. a, Staphylococcus aureus after treatment with canavalin. *C*, Control, same as *T* without treatment with canavalin. *C.E.*, Control, original culture of staphylococcus aureus. b, Colon bacillus. *T*, Subculture of colon bacillus after treatment with canavalin. *C*, Control, same as *T* without treatment with canavalin. *C.E.*, Control, original culture of colon bacillus.

posed, of course, to linear millimeter measurements). In order to determine death point, cultures of the reacting media were made at each point after completion of enzyme action. The points determined were:

Canavalin solution	Oxygen uptake
0.010 c.c.	35.0 mm.
0.030 c.c.	60.0 mm.
0.050 c.c.	95.0 mm.
0.100 c.c.	140.0 mm.

The factors of the enzyme reaction were: 0.2 cubic centimeter of colon bacillus emulsion, the washed emulsion containing nine billion living organisms per cubic centimeter; 0.5 cubic centimeter of phosphate buffer, (*p*H 7.8); water sufficient to make a total volume of 2.5 cubic centimeters. Canavalin solution in amounts stated above. Total volume of instrument (closed over all) 15.0 cubic centimeters. The instrument used was a modified Warburg.

The conclusion was that the minimum quantity of canavalin solution necessary to cause death of bacteria in the factors used was that amount which caused 60.0 millimeters of oxygen uptake. That is, death of colon bacilli occurred only at the last 3 points plotted on the curve, namely 60, 95, and 140, while the cultures taken at point No. 1 showed growth. According to this quantitative method it has been possible to prepare canavalin of ascertained "killing dosage."

It was considered desirable to compare the bactericidal power and oxygen uptake of canavalin *in vitro* with other agents which might be similar in action. For this purpose sulfadiazine and penicillin were selected. It was found to be impossible, however, to make such a comparison since sulfadiazine produces no oxygen uptake with either bacteria or polysaccharides, such as starch; penicillin in great concentration produces a slight oxygen uptake when used against bacteria with vitatropin as a co-enzyme, but in great dilution shows no reaction. If penicillin depended upon oxidation of bacteria for its evident beneficent action, one would expect some oxygen uptake in high dilution of penicillin. A weak solution of penicillin in an enzyme reaction chamber containing only bacteria emulsions and buffer solution was, however, negative for oxygen uptake.

Strangely enough while sulfadiazine gave no evidence of polysaccharide oxidation when used alone with polysaccharides there was marked stimulation of canavalin oxidation by very small quantities of sulfadiazine: e.g.—0.001 milligram of sulfadiazine in a total volume of 2.5 cubic centimeters increased the oxygen uptake of canavalin from 62.0 milli-

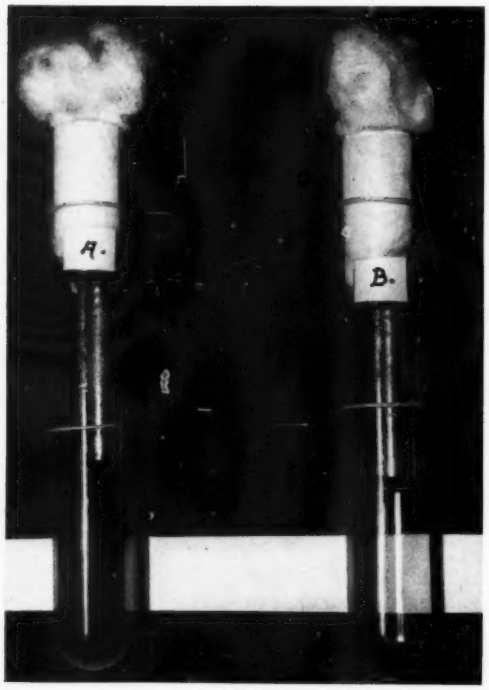

Fig. 3. Subcultures of emulsions of Staphylococcus aureus and colon bacillus, showing death of Staphylococcus aureus after treatment with canavalin. A, Colon bacillus culture (growth); B, Staphylococcus aureus (death).

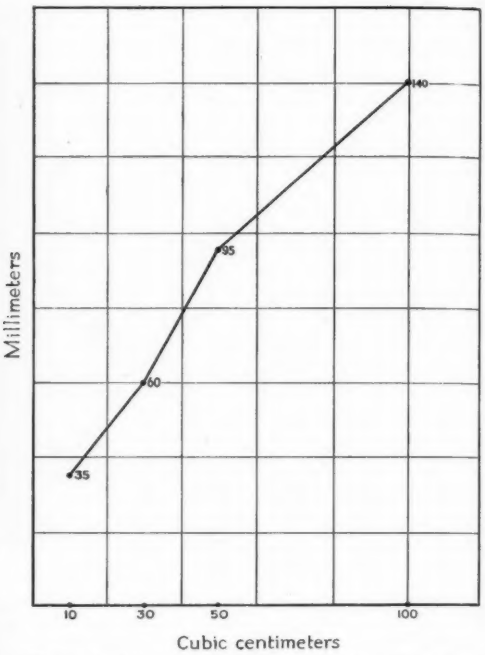

Fig. 4. Action curve of batch of canavalin. (Each space represents two.)

meters to 150.0 millimeters of partial vacuum in the reacting chamber, that is more than 100 per cent.

RESULTS OF CLINICAL USE

Canavalin, before being injected into patients, was, of course, injected in large dosage into both animals and human subjects. There was no toxic effect.

CASE 1. M. R., aged 19 years, with diagnosis of lobar pneumonia, type undetermined, was admitted to hospital January 23, 1944, with a temperature of 105 degrees F. Canavalin was administered with spectacular results. Temperature dropped from 105 degrees to normal in 12 hours and remained normal. The patient was discharged in good condition.

CASE 2. J. T., aged 38 years, with diagnosis of lobar pneumonia, pneumococcus type IV, was admitted to hospital January 24, 1944, with a temperature of 103.3 degrees F. Canavalin was administered with a drop in temperature in 24 hours to 100.2 degrees. Patient was discharged in good condition.

CASE 3. C. S., aged 19 years, with diagnosis of lobar pneumonia, pneumococcus type XXXIII, was admitted to hospital March 27, 1944, with a temperature of 105 degrees F. Canavalin was administered and there was a spectacular drop in temperature to normal. Patient was discharged in good condition.

CASE 4. E. H., aged 55 years, with diagnosis of lobar pneumonia, pneumococcus type 1, was admitted to hospital March 31, 1944, with a temperature of 104 degrees F. After treatment with canavalin the temperature dropped to 99 degrees. Next day the patient had a chill with involvement of other lung. Canavalin was again administered and the temperature dropped from 105 to 100.3 degrees. The patient seemed to be improving when she suddenly died, probably a sudden cardiac failure.

CASE 5. A. O., aged 57 years, with diagnosis of lobar pneumonia, pneumococcus type I, unresolved, was admitted to the hospital December 22, 1943, with a temperature of 102 degrees F. Patient was started on sulfadiazine, the temperature reached normal in 3 days. The patient continued in good condition for 2 days and then began to have a fever from 99 to 100 degrees F. Sulfadiazine was doubled in dosage, producing a blood level of 17.9 milligrams per cent. There followed a slow decrease of fever to normal. Sulfadiazine was stopped and the tempera-

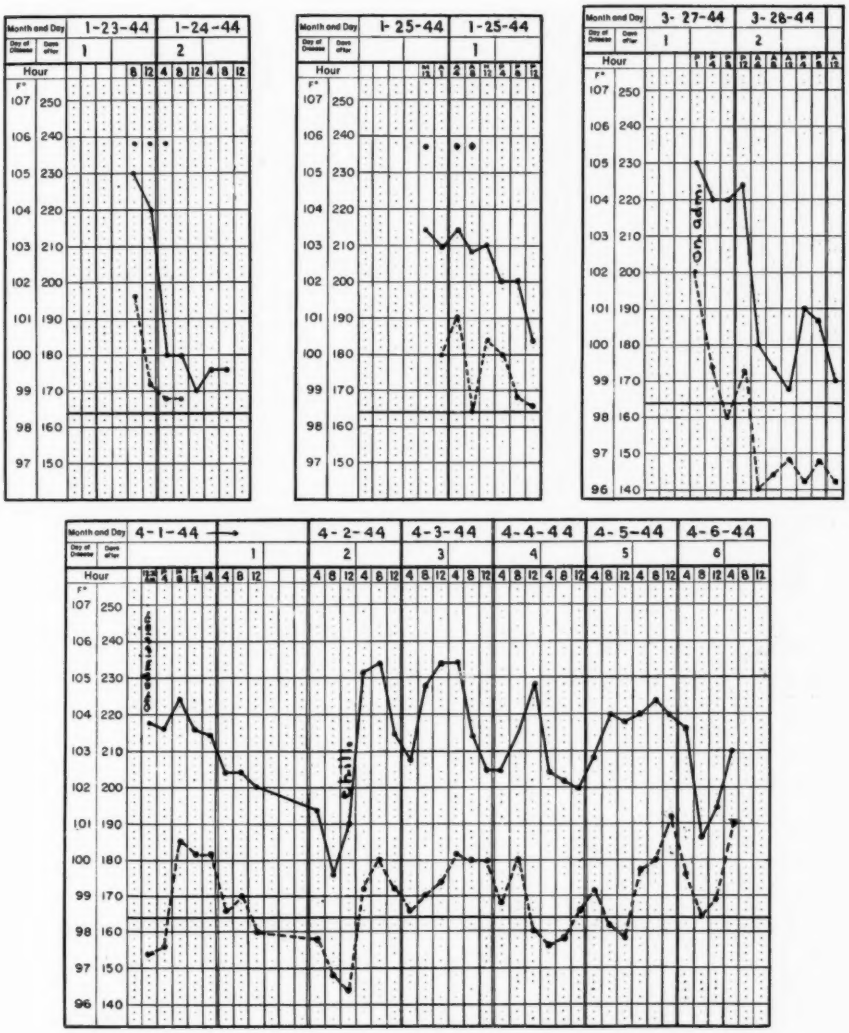

Fig. 5. The first three patients show satisfactory results: crisis in pneumonia. Patient in lower chart, aged 55 years, died of sudden heart failure after she had shown satisfactory improvement.

ture rose again. The x-ray film showed unresolved pneumonia. At this point canavalin was started. After 3 days the temperature reached normal and remained so. The patient was discharged in good condition.

CASE 6. W. M., aged 32 years, with diagnosis of lobar pneumonia, pneumococcus type XXXIII, was admitted to hospital January 17, 1944, with a temperature of 103.3 degrees F. Canavalin was administered, resulting in immediate drop in temperature to 101 degrees. Next day the temperature reached 104 degrees, whereupon administration of canavalin was repeated. The temperature immediately dropped to 100 degrees. The temperature again rose to 104 degrees and the patient was given more canavalin with a temperature drop in 2 days to normal. The temperature then remained normal and the patient was discharged in good condition.

CASE 7. D. J., aged 53 years, with diagnosis of lobar pneumonia, pneumococcus type IX, was admitted to hospital January 19, 1944, with a temperature of 104.2 degrees. This patient was given canavalin with a temperature drop in 12 hours to 100 degrees. The patient was discharged in good condition.

CASE 8. I. W., aged 32 years, with diagnosis of lobar pneumonia, pneumococcus type XII, was admitted to hospital, January 27, 1944. This patient likewise was benefited by canavalin, judging from the drop in temperature after its administration. This patient left the hospital against advice, however, and the final status is unknown.

CASE 9. W. W., aged 32 years, with diagnosis of lobar pneumonia with septicemia. This patient was treated with sulfadiazine resulting in improvement during the first 4 days. A complication, empyema, developed which remained resistant to further sulfadiazine treatment. On the 12th hospital day canavalin was started by continuous slow drop intravenous method and continued for a period of 11 days. A very large amount of canavalin (300 c.c.) was used. The temperature slowly became normal with clearing up of x-ray evidence of pulmonary disease.

CASE 10. R. T., aged 32 years, with diagnosis of lobar pneumonia, pneumococcus type I. This patient was given canavalin on admission with a spectacular drop in temperature from 105 degrees F. to normal in 12 hours. Thereafter the patient had bouts of fever for 2 days after which the temperature remained normal. The patient was discharged in good condition.

CASE 11. A. P., aged 39 years, with diagnosis of lobar pneumonia with delirium tremens. This patient was given canavalin and sulfadiazine and symptomatic treatment for delirium tremens. Negative blood culture. The patient was discharged in good condition.

CASE 12. S. H., aged 29 years, with diagnosis of lobar pneumonia, with septicemia, pneumococcus type VIII. This patient was given canavalin on admission. Her temperature promptly dropped to normal. There was a positive blood stream infection in this case, but the patient made a good recovery and was discharged in good condition.

CASE 13. C. G., aged 60 years, with diagnosis of lobar pneumonia, Staphylococcus albus. This patient had been receiving sulfadiazine without results. Canavalin was administered by intravenous slow drop method, the patient after 3 days became conscious from a comatose condition and made a slow uninterrupted recovery.

The outstanding feature of the results of treatment by canavalin of patients suffering from pneumonia was the fact that every one showed a definite drop in temperature. The temperature charts of the 3 patients showing the most spectacular results (Cases 9, 12, 13) are not included in Figure 5 because of mechanical difficulties in showing charts covering a period of such long duration. The patient in Case 9 had empyema proved by x-ray; pus was removed by paracentesis and there was a positive blood culture of type XII pneumococcus, about 40 colonies per cubic centimeter of blood. The patient in Case 12 likewise had a septicemia and recovered after treatment by canavalin. The patient in Case 13 seemed to be on the point of death, was delirious and comatose; after canavalin therapy she became conscious and made an uninterrupted recovery.

The results of the *in vitro* experiments speak for themselves. Undoubtedly canavalin does cause death of bacteria in a proper apparatus with ideal factors. Judgment as to whether canavalin will justify its beneficent clinical promise must await further trial.

SUMMARY

A new enzymatic agent has been discovered which seems to have remarkable bactericidal properties. It has been called canavalin.

Details of the methods of isolation of the enzyme and co-enzyme, which together constitute canavalin and which have the power of oxidizing polysaccharides, are given.

Canavalin *in vitro* renders both gram-positive and gram-negative organisms incapable of growth.

Report of preliminary clinical studies with canavalin are included. At present this agent seems to give promise of bactericidal properties of a superior nature.

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A HELMET FOR PROTECTION AGAINST CRANIOCEREBRAL INJURIES

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THE regular issue steel helmet worn by the American soldier admittedly furnishes excellent protection against craniocerebral injuries and what is sometimes more important to the soldier, has many other utilitarian advantages. However, it was not designed for the use of the crews of aircraft or tanks and cannot be used to advantage by them, mainly because of its size, shape, and weight. Nevertheless, the desire of a co-pilot for protection to his head from bursting 20-millimeter Oerlikon shells led him to remove the liner of his helmet and pull on the outer steel shell over his regulation leather flying helmet. The effectiveness of this protection was emphasized by the fact that his pilot, wearing only a leather helmet, was struck in the head by the fragments of an Oerlikon shell which burst between them (Fig. 1). He immediately lost consciousness, developed a left hemiplegia, and a complete left homonymous hemianopsia. While the co-pilot's helmet was punctured in several places by the high velocity fragments, it afforded complete protection from even a scalp laceration.

It became obvious that members of an aircrew needed adequate protection from craniocerebral injuries. However, any helmet designed for their use must meet certain specifications. (1) It must be close fitting and comfortable so that it will simulate as closely as possible an ordinary leather flying helmet and be considered a personal possession which might gather "good luck" like a favorite, battered felt hat. (2) It must allow free and unrestricted movements of the head in all directions, and must not interfere in any way with the field of vision. This is one of the most important objections to the use of the steel helmet pulled over a leather flying helmet. (3) It must be light in weight and afford protection from the heat and cold. (4) It must afford protection, at least equal to that afforded by the regular issue steel helmet, against craniocerebral injuries produced by fragmenting Oerlikon shells, anti-aircraft flak or concussion due to direct, blunt trauma. If these requirements can be met for aircrews the same type of helmet will serve for the use of tank crews, who at the time our study was made, wore a fiber helmet which the soldier found quite unsatisfactory for protection, efficiency, or comfort.

The percentage of wounds to the head, comparing its surface area to that of the body, is approximately 12 per cent. It was found that the larger number of craniocerebral injuries in airmen resulted from the fragmentation of 20-millimeter Oerlikon shells, followed in turn by the larger pieces of antiaircraft flak and concussion due to direct trauma. When an Oerlikon shell bursts it fragments into thousands of pieces which vary in weight from less than 1 milligram to 20 grams. However, the largest number of "effective" Oerlikon shell fragments bursting in an area 5 feet in diameter and capable of causing incapacitation to the person exposed is 260. The majority of these 260 fragments weigh between 10 and 50 milligrams and their velocity varies between 400 and 600 meters per second (Fig. 2).

Many materials were suggested and subjected to accurate ballistic and other tests. It was finally concluded that an acrylic resin, properly manufactured, offered the largest number of advantages for the purpose and most closely met the

Fig. 1. Roentgenogram of skull showing fragments of Oerlikon 20-millimeter shell embedded in the right parieto-occipital cerebral cortex.

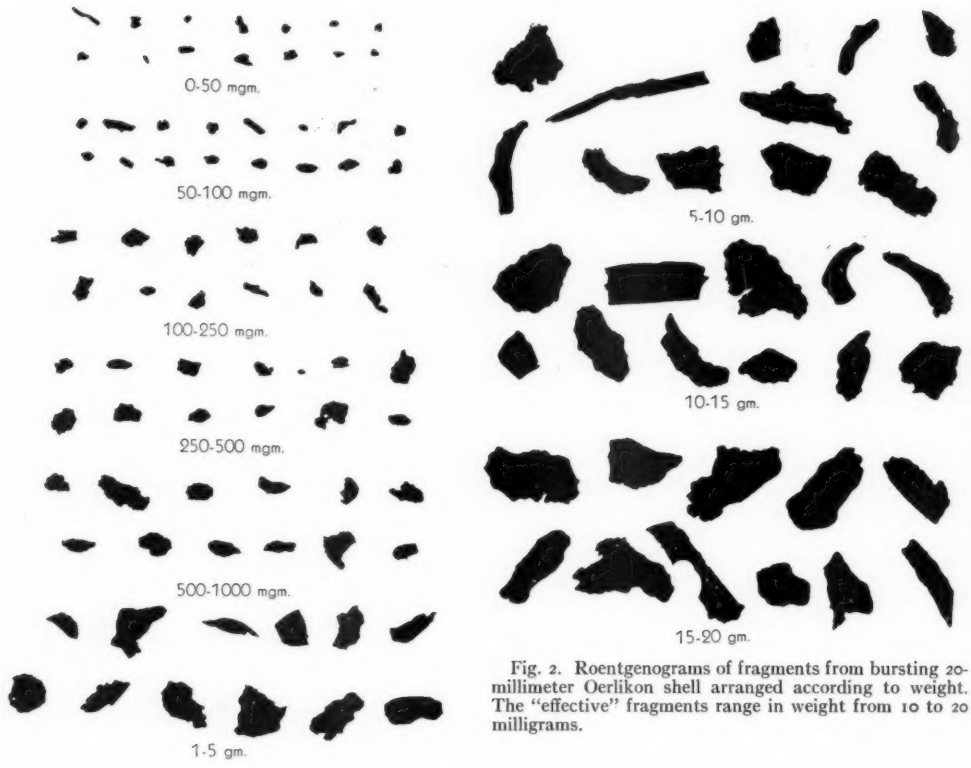

Fig. 2. Roentgenograms of fragments from bursting 20-millimeter Oerlikon shell arranged according to weight. The "effective" fragments range in weight from 10 to 20 milligrams.

specifications laid down.[1] This material of 4-millimeter thickness has a velocity resistance in relation to its weight per unit area of 440 meters per second when tested with a 52-milligram steel ball fired and photographed electrically. The velocity resistance per unit weight area of the same material of 8-millimeter thickness, similarly tested, is 700 meters per second. Velocity resistance per unit weight area of 1-millimeter thickness manganese steel tested under identical circumstances varies from 400 to 600 meters per second.

The acrylic resin studied has a tensile strength of from 9,000 to 12,000 pounds per square inch; a flexural strength of 12,000 to 14,000 pounds per square inch; an impact resistance of 0.1 to 0.3 foot pounds and a Brinell hardness greater than gold. It has a specific gravity of 1.10, so that it almost floats on water, and it will absorb less than 0.5 per cent of water by weight upon immersion for 7 days. It is resistant to the rays of the sun and will not soften until a temperature of between 190 and 240 degrees F. has been reached. In fact, it is one of the best nonconductors of heat and cold known to science. It smoulders if a flame is applied to it but it will not burn with an explosion and, if it flames, the slightest movement extinguishes it. When hit directly the lines of shatter of this material are at right angles to the force and not directly forward as in steel. Experimental and clinical studies have shown that if pieces of it are driven into or buried in the brain or soft tissues it is inert, and there is no serious tissue reaction.

A model helmet was made by heating and molding flat pieces of acrylic resin to conform to the frontal, temporal, occipital and vertex portions of the skull. These segments were hinged together snugly so that protection would not be lost and yet so that a certain pliability would be gained and a sense of a solid, bucket-like structure would be avoided. This protective helmet was then cov-

[1]It must be remembered that there are almost unending variations of the stages which can be reached in the manufacture of the products of an acrylic resin. The properties of the final product may vary within extremely wide limits so that one may think of it as a substitute for glass, a denture, a surgical suture or a putty-like material. By modifying the amount or character of the plasticizer added, the flexibility, resiliency, hardness, water and weather resistance, inflammability, and ballistic properties of the material can be varied at will between very wide limits.

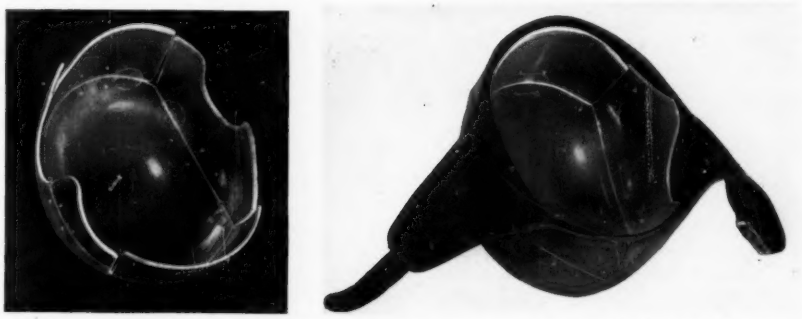

Fig. 3. a, left, Fabricated and segmented acrylic resin protective liner for helmet; b, protective liner within ordinary leather flying helmet.

ered with the commonly used regulation leather flying helmet and lined with chamois skin or fleece. Portions of the acrylic resin material were brought down over the ears and openings left into which earphones could be fitted. This afforded further protection and added the distinct advantage of the property of acrylic resin to exclude ambient noises (Fig. 3).

A helmet so constructed allows for complete movement of the head in all directions, provides complete protection over the frontal and occipital areas, and in no way interferes with the field of vision. As one molds a derby hat which may impinge slightly upon the parietal eminences and be uncomfortable so can the individual wearer mold this type of helmet by applying heat to the protective liner so that it becomes an integral and comfortable part of him. Such a model helmet constructed of acrylic resin 4 millimeters in thickness, covered and lined as described, weighs 18 ounces and if 8-millimeter thickness material is used, thus affording more protection per unit weight area, the total weight of the helmet is raised to 27 ounces. The steel body of the regulation helmet weighs 35.84 ounces. The use of an acrylic resin product obviates the necessity of using steel with its high priority demands for other purposes and provides a less expensive material, which can be fabricated quickly and without the expensive manufacturing accessories.

The extension of the use of this same material in the form of panels which can be easily inserted into and removed from an airman's protective clothing and thus provide lightweight body armor for protection against chest, abdominal, and extremity injuries is logical.

SURGERY OF THE PELVIC COLON AND RECTUM

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WITH the co-operation of our tumor clinic we have classified those patients treated the past seven years at the Mason Clinic for surgical lesions of the colon and rectum.[1] These lesions have been subdivided into those of (1) the right colon; (2) the transverse colon; (3) the left colon, including the upper sigmoid; and (4) the pelvic colon, i.e., the lower sigmoid and rectum. This report will be confined to the fourth group. The lower sigmoid is grouped with the rectosigmoid because in each instance resection required either permanent colostomy or the single alternative of rectocolic anastomosis deep in the pelvis—a technically difficult if not hazardous procedure. That portion of the redundant or upper sigmoid which permits of exteriorization resection is not included in this report.

Of 195 patients, 111 had lesions of the pelvic colon or rectum (Table I). Ninety-nine of the 111 were carcinoma, while 12 required major surgery for lesions other than carcinoma. An analysis of these 12 is tabulated in Table II.

NON-SPECIFIC GRANULOMAS

Stenosing inflammatory granulomas may cause complete obstruction of the colon and may be grossly indistinguishable from cancer even after the abdomen is opened. There were 4 instances of this in the pelvic colon; 2 required a combined resection, while in 2 an anterior resection with anastomosis was done. In each of these (Figs. 1 and 2) because of fever and extensive local fixation at the rectosigmoid, the resection was accomplished in 2 stages; in each the resection was difficult despite marked recession of the tumor between stages and in each stenosis was practically complete, and in 3 of the 4 the true diagnosis was unpredicted before histological examination. The etiology in these 3 remains undetermined, a Frei antigen test for granuloma venerum was negative; in 1 there were associated diverticula. In a 4th case a sleeve of lower sigmoid had become directly involved from contact with a prolapsed loop of terminal ileitis. And this hoselike sleeve of colon had to be resected secondarily after resection of the terminal ileum and cecum. Parenthetically, this patient made a complete recovery, was commissioned a captain in the army, and died in action in the battle of Tunisia.

Diverticulitis as a cause for stenosis of a sleeve of colon is well recognized. However, the fact that cancer may occur simultaneously with diverticulosis may not be as well appreciated. Such was the case in 1 man, aged 73 years, diagnosed elsewhere just before admission to the hospital as diverticulitis (Fig. 3) and given only medical recommendations. At operation a large local *cancer*, involving this portion of the lower sigmoid, and adherent to one loop of small bowel (Figs. 4 and 5) was found. A one stage resection of small and large bowel, with small and large bowel primary anastomosis was accomplished, the patient being discharged from the hospital after 18 days.

OBSTRUCTING ENDOMETRIOMA

There were 2 cases in which an endometrioma obstructed the lower sigmoid. In one of these an anterior resection with anastomosis was accomplished, and in the other a temporary colostomy and resection of the ovaries was done.

CARCINOMA OF PELVIC COLON

There were 99 patients with cancer of the pelvic colon who came to surgery (Table III). Surgical assistance was limited to palliative colostomy in 21 of these, while in 6 the lesion was too advanced to justify even this. Two were given palliative relief from bleeding by diathermization. Three others were "cured" by diathermization. This leaves 67 whose lesions were resected surgically; of this group 5 already had distant metastasis. Excluding the 3 who had "curative" diathermization, and including 2 moribund patients not operated upon, the *resectability* in the series was therefore 66 per cent.[2] The surgical mortality was 5 per cent overall, 3.8 per cent for those resected.

The follow-up on the majority is too short to be of value. Of the 49 combined resections 7 (14 per cent) have died of metastases, 4 of unrelated causes, and 2 cannot be followed: 73 per cent are known to be living and well. Of the 7 posterior resections 4 are known to have died of carcinoma, and 2 cannot be followed. The compromising in-

From the Department of Surgery, The Mason Clinic. Delivered before the North Pacific Surgical Society at its annual meeting, Vancouver, B. C., November 20, 1943.

[1] All operations in this review were performed by either Dr. E. B. Potter, C. S. Stone, Jr., or the author.

[2] Nine who refused operation or went elsewhere are not included.

adequacy of the posterior resection is now felt by all workers in this field. The anterior resections have all been done within the past 15 months: all but 1 are living. The patient who died, and 3 others, had hepatic metastasis at the time of resection.

PLACE OF DIATHERMIZATION

Diathermization is a compromising procedure. It does not remove nor does it permit examination of the regional lymphatics. However, if one has the proper equipment and understands its limitations, diathermization is a valuable aid in managing a small minority of patients. It allays bleeding, cleans the infected sloughing surface of the ulcer, and may be attended by temporary clinical improvement in strength and well-being. In 1 patient, age 81 years, feeble, bleeding, and toxic, the improvement after 6 weeks was so great that he successfully underwent a combined Miles resection (Fig. 6). Histologically, his growth was a *colloid* adenocarcinoma (Fig. 7) and this may explain the fact that it did not completely recede with diathermization—and hence the necessity for a combined resection. In 3 patients, in their 8th decade of life, all obese and feeble, with proctoscopically accessible lesions varying in size from 1.5 inches to 2.5 inches in diameter, surgical diathermization was substituted for surgical resection. One of these lived 5 years and died of a broken hip; another 6 years and died of acute coronary thrombosis—each without evidence of local recurrence or metastasis. The 3rd is living and well 3 years since treatment, and without evidence of carcinoma.

We therefore feel that the procedure justifies consideration in certain patients whose lesions are technically accessible, and who are adjudged to be hopeless surgical risks. Preservation of normal bowel continuity is *not* a justification for its use.

TABLE I.—SURGICAL LESIONS OF COLON: MASON CLINIC

(1936–1943) Site of lesion	No. patients	No. operations	Patient mortality
Right colon	33—13*	47	1
Transverse colon	8	11	0
Descending colon (including upper sigmoid)	43—11*	71	8—4 of 8‡
Pelvic colon and rectum	111—12*	166	5—2 of 5‡
Totals	195	295	14—6 of 11‡

*Patients having surgical lesions other than cancer.
‡Death following palliative colostomy only.

THE COMBINED RESECTION

It is our experience that this must be considered the preferable surgical attack both from the standpoint of surgical mortality and the theoretical eradication of the maximum of local tissue environment and regional lymphatics. The only disadvantage is the loss of anorectal function, which loss is well compensated by the high percentage of cure being reported from all authors engaged in this special work. The reported mortality is being steadily reduced.

It should be remembered that lesions arising in the pectinate line may be adenocarcinoma (Fig. 8) or more rarely epidermoid carcinoma (Fig. 9). The inguinal lymphatics should be carefully examined for metastasis in lesions arising this low. Unfortunately, some may seek advice too late (Fig. 10).

Of 49 combined resections for primary carcinoma, and including an additional 3 for other lesions, there was but 1 hospital death. It is with hesitancy that we mention this low mortality because of the limited size of the series. Interestingly enough, it was not our first but the 49th of the series of 52 who died. The patient, aged 66

TABLE II.—PELVIC COLON—SURGICAL LESIONS OTHER THAN CANCER

No. of pts.	Pathological lesion	Operation	Deaths
4	Stenosing "granuloma"	2 Combined abdominoperineal 2 Anterior resection with anastomosis	0 0
1	Ovarian carcinoma recurrent in rectum	Combined abdominoperineal	0
2	Benign polyp lower sigmoid	Sigmoidotomy	0
2	Obstructing endometrioma	1 anterior resection with anastomosis 1 Temporary colostomy and resection of ovaries	0 0
1	Proctoscopic perforation	Laparotomy closure	0
1	Acute suppurative diverticulitis	Temporary defunctioning colostomy	0
1	Surgical fistula during prostatectomy	Temporary colostomy	0
12			

Fig. 1.

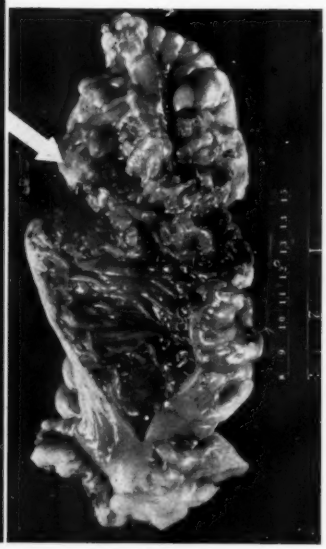


Fig. 2.

Fig. 3.

Figs. 1 and 2. Photographs of benign stenosing granulomas involving the lower sigmoid. Each was associated with a febrile course and complete obstruction, hence resection was done in two stages—a combined in the one, and anterior resection with restoration of continuity in the other.

Fig. 3. Roentgenogram demonstrating a case of diverticulosis of the descending and sigmoid colon associated with carcinoma of the sigmoid.

years, had been out of bed 4 days; sudden death on the 10th postoperative day was adjudged clinically as due to pulmonary embolism. Ages of those resected varied from 29 to 81 years.

The procedure as first advocated by Miles (3) is well standardized; however, various authors have contributed minor variations in technique and after-care which have been helpful; some of these alternatives prove adaptable to one surgeon while others appeal to another. Perhaps therefore we should mention our preferences—although the fact that in this brief experience we have come to favor certain modifications and to discard others does not imply that the same should prove true in other hands.

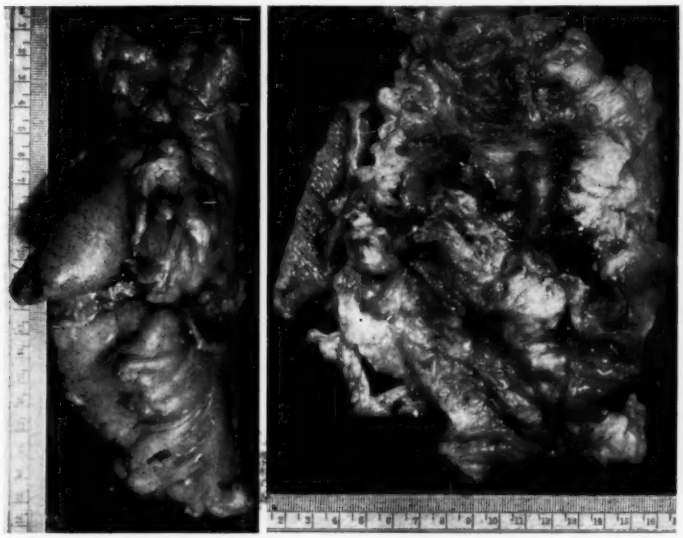
1. As a working rule we prefer the *one* stage procedure as advocated by Miles. Of the 52 cases, only 13 were accomplished in 2 stages. Advanced obstruction not relieved adequately by cecostomy, or a febrile course secondary to superimposed local infection constitute in our opinion the only contraindication to a one stage resection. Advanced age and impaired surgical risk are not indications for putting the patient through 2 operations to accomplish what can be accomplished with greater technical ease in one.

2. General inhalation anesthesia is preferred.

3. A lower midline or lower left rectus splitting incision is made; with the permanent colostomy to be made through a separate carefully placed left lower gridiron incision.

To prevent skin stricture Miles modified his original technique by removing an oval of skin about the colostomy. We have had 5 skin strictures despite this, but feel that this modification reduces the incidence of stricture. Because of 2 lateral fistulas in the colostomy stump, secondary to perforation of the edematous bowel by the sharp edge of the external oblique aponeurosis, we now also *remove an elliptical wedge of this fascia* on either side of the colon. In addition, we carefully visualize each layer as the incision is made, rather than trust to the quicker blind stab. The opening in the left lateral gutter between the mesentery and the abdominal parietes is closed to prevent volvulus of the small gut.

4. The perineal wound is packed open with a rubber dam into which gauze is loosely placed. For



Figs. 4 and 5. An exterior and interior view of the involved sleeve of sigmoid shown roentgenologically in Figure 3. It is to be noted that this annular ulcerative adenocarcinoma had invaded a loop of small bowel which was resected *en bloc* with the sigmoid. Double primary intestinal anastomosis was done.

faster healing it is important to build as redundant a pelvic peritoneal diaphragm as possible. In the male this is accomplished with greater ease by freeing the peritoneum from the bladder. After the pack is removed irrigation with an emulsion of sulfacarbamide seems to speed third intention healing. It is beneficial to get the patient out of bed early—in 6 or 7 days, if possible.

5. We have not used sulfasuxidine or sulfaguanidine in preparation for the combined operation, but we do use now a combination of sulfathiazole and sulfanilamide microcrystals locally between the omentum and the parietal peritoneum, and in the abdominal and perineal wounds.

6. A blood transfusion is given routinely during the operation and multiple transfusions if the patient is anemic. Vitamin C and B complex are given parenterally, although the administration of the B complex is delayed for 5 days after operation so that it will not inhibit the action of the sulfa drug.

7. The colostomy clamp is removed at the end of 24 hours; to leave it longer, may accentuate the abdominal distention and could favor separation of the peritoneal adherence around the colon. A dry gauze, collared around the exteriorized colostomy stump at the time of operation is left for from 4 to 5 days as a safeguard against retraction of the colon.

8. The duration of life for 3 years or more, in a few patients with hepatic metastasis has encouraged us to resect some lesions despite one or two distant metastases. It has also been consoling to cite these instances in reporting such involvement to the patient or his family. It should also be mentioned that in 2 proven instances what we had adjudged by palpation at operation to be a solitary hepatic metastasis proved to be a solitary congenital cyst near the surface of the liver (Fig. 11). In each of these instances a radical resection was performed, and autopsy following unrelated death (postoperative embolus; perforated gastric ulcer) later proved the fallacy of the operative impression.

TABLE III.—CANCER OF PELVIC COLON AND RECTUM

No. of pts.	Type of operation	Patient mortality
21	Palliative colostomy	2 (cachexia)
6	Exploration only	0
2	Palliative diathermy	0
3	"Curative" diathermy	0
67 (49)	Combined abdominoperineal resection	1 (embolus)
67 (7)	Colostomy and posterior resection	0
67 (9)	Anterior resection with anastomosis	1 (embolus)
67 (2)	Anterior resection with colostomy	1 (heart)
99		5 (5.05%)

Fig. 6. Photograph of a colloid adenocarcinoma resected by the combined approach in a man aged 81 years. Six weeks previous to resection he had several applications of diathermy to the ulcer.

This certainly should be borne in mind before a radical resection is withheld in the face of what is thought to be a hepatic metastasis.

9. We have been pleasantly surprised with the ability of some of these patients to withstand ex-

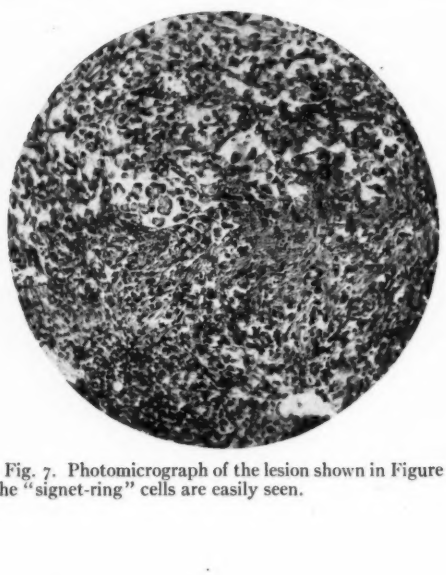


Fig. 7. Photomicrograph of the lesion shown in Figure 6. The "signet-ring" cells are easily seen.

Fig. 8. Photograph of an adenocarcinoma of the sphincteric region of the anus. There was no demonstrable inguinal lymphatic metastasis.

tensive resections of what at first appeared to be a locally inoperable growth.

In 1 patient a coincident (Fig. 12) cystadenocarcinoma of the ovary was grown to the sigmoid and was therefore resected *en bloc* along with the cancer of the rectum. In this series 2 patients had associated cancer of the ovary, 2 had had cancer of the breast, and 1 had had cancer of the uterine fundus.

One of the most hazardous was this case (Fig. 13) in which a *4 months' fever* and anemia from superimposed infection persisted for 6 weeks after a first stage Lahey colostomy. At the second stage, resection of a loop of adherent ileum was required as a preliminary to the combined removal of the rectum, and freeing the local growth with a margin was difficult. As is often true, the most difficult in the amphitheater runs the smoothest convalescence—thus affording a stimulus to increasingly broaden resectability.

MUCOSAL POLYPS

There were 2 instances of single, large, pedunculated polyps just above the rectosigmoid (Fig. 14), which were inaccessible via the sigmoidoscope. The advantage of contrast media in roent-

Fig. 9a. Photograph of an epidermoid carcinoma of the sphincteric region of the anus. Bilaterally enlarged inguinal lymph nodes led to a bilateral radical resection of the inguinal lymphatics, but no positive nodes were found.

genological diagnosis of these is recognized. One of these was removed by one stage abdominal sigmoidotomy with simple closure of the gut; the other by colostomy and subsequent closure in 2 stages. During this same period there were *68 patients* (not included in the statistical table) with one or more polyps which were removed, and the rectum diathermized through the sigmoidoscope. Ten of these 68 showed hyperplasia at the tip graded as "adenocarcinoma grade I."[1]

The malignant potentiality of *all* colonic mucosal polyps is now recognized. In this series of 159 malignant neoplasms there are 6 instances of double malignant lesions of the colon, and one of a triple malignant lesion. In several lesions there were satellite benign polyps (Fig. 15).

When the polyp showing borderline malignant hyperplasia has a long benign pedicle, or when a small sessile polyp without definite malignant change is *without ulceration* or *palpable indurated invasion*, we have been satisfied with marginal removal and diathermization via the proctoscope. Of the 10 showing borderline malignant changes so treated, 2 did not return and the other 8 have shown no trace of recurrence.

[1]Since this review was delivered 2 months ago we now have in the hospital a patient whose case clearly illustrates the malignant potentiality of mucosal polyps. This man, aged 60 years, was examined in the clinic 5 years ago, at which time an incidental finding was a mucosal polyp, 1 centimeter in diameter, seated in the rectal ampulla. He was to return the following week for removal of the polyp and diathermization. He did not return until 5 years later, at which time he is found to have an annular adenocarcinoma at the exact site at which the polyp was previously described.

Fig. 10. Photograph of an inoperable adenocarcinoma of the anus with extensive involvement of the buttocks.

It should be emphatically repeated, however, that the invasive polypoid lesion with or without ulceration requires radical resection of the gut and its regional lymphatics. The smaller or earlier the lesion, the more the reason for a wide resection as these patients afford the greater opportunity for cure. Figure 16 is a photograph of the smallest lesion we have been required to resect radically. In another instance of a large sized benign polyp requiring laparotomy for removal, it was thought preferable to resect the sleeve of gut rather than simply to remove the polyp.

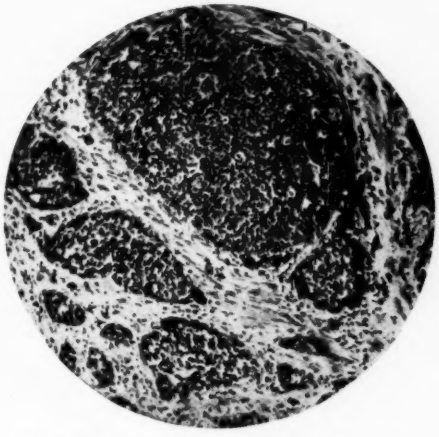


Fig. 9b. Photomicrograph of lesion in Figure 9a.

Fig. 11.

Fig. 11. Photograph of a congenital solitary cyst of the liver which at the time of surgical exploration was thought by palpation to be a hepatic metastasis. This possibility should be borne in mind at the time of exploration. This patient died 3 years after surgical resection from an unrelated cause and the specimen was photographed at necropsy.

Fig. 12. Photograph of a carcinoma of the rectum (lower arrow) associated with a coincident carcinoma of the ovary which has secondarily invaded the rectosigmoid (upper arrow).

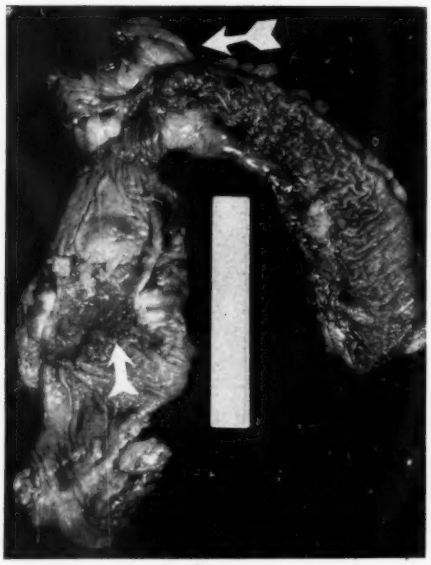


Fig. 12.

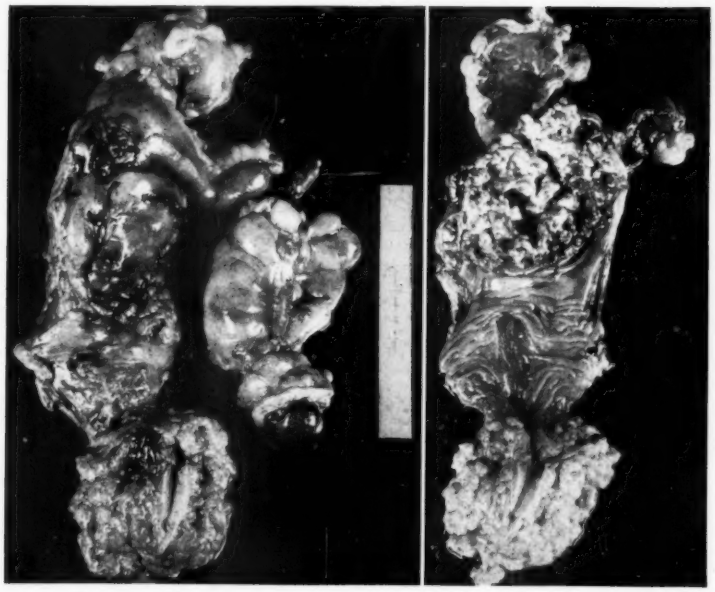
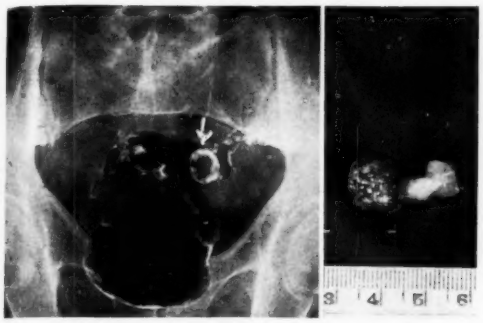


Fig. 13. Exterior and interior photograph of an extensive carcinoma of the rectosigmoid with secondary invasion of a loop of small bowel. A preoperative febrile course which did not subside following a first stage colostomy is explained by the degeneration and superimposed infection, which are visible in the growth.



a b

Fig. 14. a, Roentgenogram with contrast media depicting a solitary polyp of the sigmoid. b, Photograph of the same polyp after removal by one stage sigmoidotomy. c, Photomicrograph of the same lesion.

Fig. 14c.

Fig. 15, left. Adenocarcinoma of the ampulla of the rectum associated with multiple satellite benign polyps (arrows).

Fig. 16. Photograph of the smallest adenocarcinoma for which we have performed a proctosigmoidectomy. (Lateral view of the opened rectum—see arrow.)

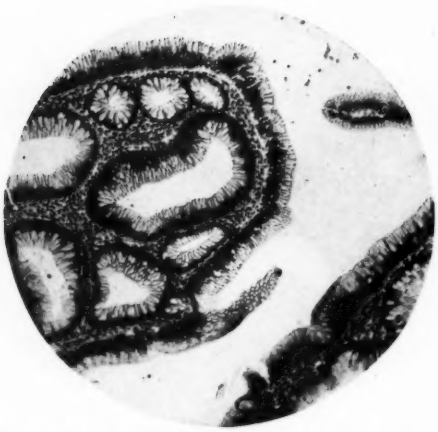


Fig. 17. a, left, Preoperative biopsy of sessile polypoid rectal lesion which shows no evidence of malignancy. b, Photomicrograph of the same lesion after removal showing adenocarcinoma.

A case specifically illustrating this differential problem is that of an attractive 31 year old wife who had a sessile polypoid lesion, 3 centimeters in diameter, in the upper ampulla. Three biopsies failed to show malignancy (Fig. 17a). Despite this fact, and because of its grossly invasive appearance, we elected—against the advice of some —to resect radically this bowel and its regional lymphatics (Fig. 18). Because this patient was thin and with a large true pelvis, we were able to accomplish an exceptionally low primary anastomosis and thereby preserve bowel continuity. The responsibility in such a disputed case of needlessly sacrificing rectal function is second only to the responsibility of sacrificing life, either from inadequate resection of cancer, or from a surgical mortality in a technically hazardous procedure. The removed specimen showed cancer (Fig. 17b).

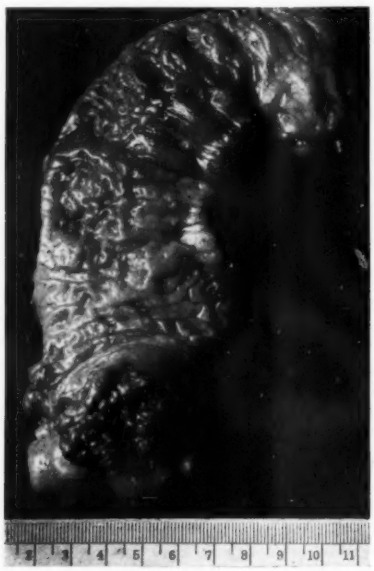


Fig. 18. Photograph of the gross lesion shown in Fig. 17.

On the other hand, a benign lesion, which may be mistaken for an invading sessile cancer, is the submucosal lymphoid tumor referred to as a "rectal tonsil." In one young lady the disc-shaped tumor was 3 centimeters in diameter and 1 centimeter in thickness and, before biopsy revealed its true nature, it was thought to be malignant.

ANTERIOR RESECTION OF THE PELVIC COLON WITH PRIMARY ANASTOMOSIS

Miles in 1908 published his conception of the lymphatic spread of cancer of the rectum upward, downward, and laterally. Supported by his excellent results with the combined operation this won universal adoption to the point that anything less radical has come to be considered a compromising procedure. However, Westheus recently has taken issue with Miles as to the downward lymphatic spread. In 102 operative specimens removed by radical abdominal perineal resection he found 210 metastatic nodes. *Only one* of these was located below the level of the lower edge of the growth. Coller and associates and Gilchrist

and David have also made studies indicating that lymphatic metastasis is upward in the great majority of instances. *It would seem probable that the spread is downward only when extensive lymphatic involvement blockades the upward path.* If this is true then it would seem that certain low sigmoidal and rectosigmoidal lesions may be adequately resected without sacrificing continuity of the lower bowel.

Since the procedure of primarily anastomosing the colon this low in the pelvis is technically difficult, and because many authors still question its adequacy, we were loath to use it until recently. The first two trials were in patients with several metastatic areas in the liver. We have now performed 9 anterior abdominal resections of the pelvic colon with one stage primary anastomosis of the sigmoid to the rectal ampulla. Four of these were palliative resections. There was 1 death—this from a pulmonary embolus (verified by autopsy) on the 14th day in an otherwise uncomplicated course, the wound having healed *per primam* without fistula: the source of the embolus proving to be an acute thrombosis of superficial varicose veins in the right leg.

In 2 additional poor risk patients anterior resection was supplemented by closing the ampulla and bringing out the proximal bowel, including the tumor, as a permanent colostomy. In 1 of these patients, short of statue and weighing 275 pounds, an anastomosis would have been definitely hazardous; in the other, because of extensive lymphatic metastasis, the left colic artery had to be resected, and hence the entire descending and pelvic colon; and it was deemed inadvisable to prolong the operation further by anastomosis. This patient died on the 7th postoperative day, the cause of death being undetermined. In a 12th patient who had an obstructing endometrioma, the rectosigmoid was resected and anastomosis was done in stages after a defunctioning temporary ileostomy.

In this brief experience we have found no surgical objection to anastomosing the pelvic colon. It is difficult in a small pelvis; it requires the same time as the combined operation, but the hospitalization period is shortened as compared with the combined operation. We have tried the closed and open technique and prefer the latter. Such anastomosis should not be attempted in the obstructed bowel without preliminary surgical defunction. Here as in any intestinal anastomosis peritonitis and death are not so likely from operative soiling as from subsequent leakage in an inaccurate anastomosis. In 4 instances concomitant tube cecostomy was performed. These have closed

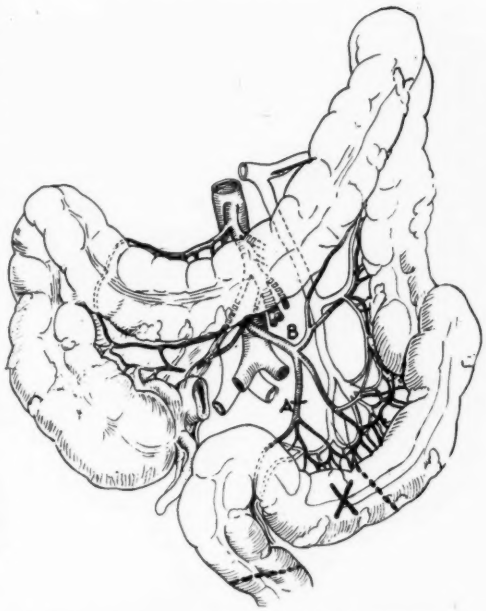


Fig. 19. Diagrammatic showing of the circulation of the colon. "*X*" marks the zone wherein one must be careful to insure adequate circulation of the end of the sigmoid if a rectosigmoid anastomosis is done.

spontaneously, without prolonging hospitalization or causing inconvenience to the patient, but their course has seemed no smoother than that of those in which it was not done. Nor has a rectal tube been used beyond the anastomosis. Usually the anastomosis is sufficiently low that a rectal finger can be used to explore beyond it, or pass a tube if this should prove to advantage postoperatively. A hard tube at the anastomosis might serve rather to obstruct the lumen and impair healing in a colon which has not been defunctioned. Obviously, this series is too small for conclusions to be drawn.

Regardless of how short the cuff of remaining ampulla, one need not worry about its blood supply as the middle and inferior hemorrhoidal artery, or even the latter alone, apparently suffices to supply this segment. But this is not true of the proximal end. Radical resection, just as in the combined operation, requires section of the superior hemorrhoidal vessels: this leaves a danger zone between this level and that supplied by the sigmoidal arteries (Fig. 19). One of the technical niceties of the procedure is freeing the gut ends of fat to permit accurate sutures without sacrificing

the terminal arterial supply, and this seems better accomplished in the open technique. In the closed technique the Harvey Stone or the McClure-Furniss clamps are most helpful.

It should be remembered that the ampulla, having no serosal investment, is slow to heal. Because of this, secondary leakage may be expected and planned for. We build a peritoneal diaphragm about the anastomosis, and a Penrose drain is left behind the anastomosis in the presacral area. Four of the 9 developed temporary fecal fistulas, none showed evidence of peritonitis, and in all the fistulas healed spontaneously in from 2 to 8 weeks. The patient was not kept in the hospital additional time because of the fistula.

One patient had periods of diarrhea attributed to narrowing at the anastomosis. However, a rectal finger passes the anastomosis easily. This patient, aged 68 years, required resection and anastomosis of the small and large bowel and hysterectomy (because of local extension)—all accomplished in one stage. Despite the occasional diarrhea she has gained 26 pounds in weight, and is otherwise symptomfree.

SUMMARY

1. An analytical review of 111 patients requiring major surgery for lesions of the pelvic colon is presented. Ninety-nine of these were carcinoma.

2. Resectability of the malignant lesion was 66 per cent: overall hospital mortality 5 per cent.

3. The combined resection was the most commonly applied, although in the past 18 months some anterior radical resections with primary anastomosis have been done.

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AN EXPERIMENTAL AND CLINICAL STUDY ON THE USE OF ADULT ANIMAL TISSUE EXTRACT IN THE ACCELERATION OF WOUND HEALING

A Preliminary Report

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IT is well known that the organism, from the lowest form of life to the most complex, has the power of tissue repair, a cycle of events beginning with injury and ceasing when the reparative processes are completed. In man, the ability of an open wound to heal with organ-specific tissue is a remarkable example of this fundamental law of biology. It has long been suspected that in all tissue there are two important mechanisms concerned with repair, namely, growth inhibiting and growth promoting factors. It is with the latter that this communication primarily deals, particularly in its practical application to wound healing—an ever current problem to the surgeon.

REVIEW

In 1925 Baker and Carrel (1) reported that embryo-web porridge was effective in accelerating wound healing both *in vivo* and *in vitro*, and following this Fischer produced an embryonic extract which stimulated growth *in vitro* and was apparently successful when used in animals and man.

From 1925 to 1932 other workers (2, 3, 14, 17, 19, 20, 22) demonstrated the growth accelerating effect of embryonic juices on wounds, but because of its impracticability this method of treating wounds was little used. Interest, however, was revived in 1939 and 1940 when Fischer prepared a modified, desiccated embryonic extract which was used in animal experiments by Nielsen and clinically by Waugh.

Prior to 1939, growth promoting substances were prepared primarily from embryonic tissue because it was felt that such factors which might promote growth would be present in greater amounts, although extracts of tissues and organs of adult animals had occasionally been used as constituents of tissue culture media. In these cases extracts from mitotically active or neoplastic tissues, such as bone marrow and tumors, were used. However, the growth promoting activity of these extracts was always regarded as much less than that of embryonic extract (15, 16, 21).

In 1939 it was shown by Hoffman and Doljanski (11) that extracts of tissues and organs of adult fowl increased the growth rate of chicken fibroblasts *in vitro* to a remarkable extent, completely independent of the degree of differentiation of the tissue which was extracted. It was found that most activity was present in brain, heart, and smooth muscle, all of which are stable adult tissues (12, 13). It was further shown that adult tissue extract from chickens had a greater stimulating effect on the growth of chicken fibroblasts than did embryonic extracts. In a series of experiments comparing the cell growth stimulating action of aqueous extracts of heart (adult) tissue, it was shown that the former had a growth promoting effect about three times as great as that of embryonic extract. This effect was not found to be transitory as previously believed, since tissues may be cultivated indefinitely in media containing adult extracts (5). Also, it was shown that the growth promoting action of adult tissue juices is not species specific inasmuch as extracts of heart muscle of calf, sheep, rabbit, and dog had a cell growth promoting effect of the same order and magnitude on chicken fibroblasts as homologous tissue extract. Finally, it was found (6) that explanted human epithelium *in vitro* had a growth about 16 times as great when adult chicken heart extract was added to the usual protective media (plasma and Tyrode solution). This fact, and for the reasons that it is more stable and more easily obtainable, suggested that adult tissue extract might be of value in promoting growth of tissue in human wounds. Schloss[1], working at the Hadassah Hospital in Jerusalem in 1942, used adult tissue extract in the treatment of indolent human wounds with encouraging results, and it was further to try this

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[1]Personal communication.

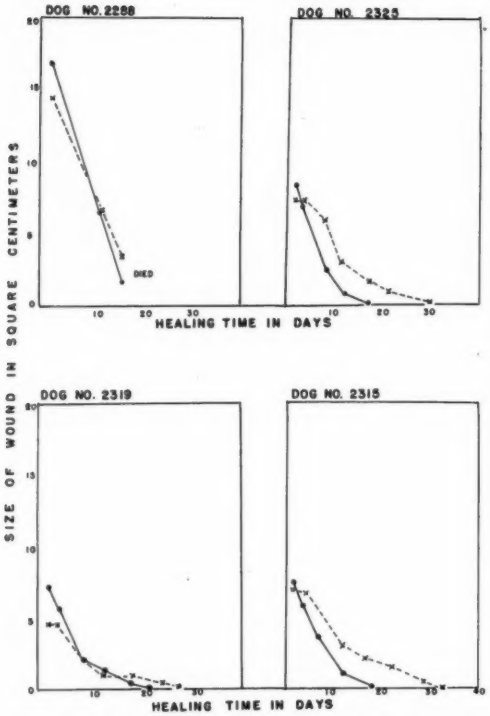

Fig. 1. Graphs showing 4 of the animal experiments. Note that the treated curves (straight lines) cross the control curves (crossed lines) early in the course of treatment. This is suggestive of the fact that tissue extract may influence granulation tissue as well as final epidermization.

effect that the following laboratory and clinical experiments were done.

The material to be tested was prepared as follows: Sterile adult sheep hearts were cut up and placed in a blender with Tyrode solution and finely minced. This mixture was allowed to stand in the refrigerator for approximately 24 hours, and then centrifuged. The supernatant fluid was decanted and placed in convenient sterile flasks. This extract, when kept in the icebox, was found to maintain its growth promoting activity for at least 1 month. The growth accelerating properties of these extracts were tested from time to time on cells growing *in vitro* by a standardized method.

EXPERIMENTAL STUDY

Normal healthy mongrel dogs of either sex and of any age were used as experimental animals. Under intravenous nembutal anesthesia, symmetrical, bilateral circular areas of skin were excised on either side of the lower chest, in some instances with sterile precautions and in others not. All bleeding points were clamped and tied with fine silk, and sterile gauze dressings were applied. At the outset it was obvious that great difficulty would be encountered in maintaining intact dressings over these lesions in active animals. Bandage and tape were found inadequate and when reinforced with fenestrated plaster jackets, interfered with the animal's nutrition, respiration, and other vital functions. Finally, a method was devised which consisted of using Michel skin clips to hold the dressing to the animal's skin, and covering this with elastic (Ace) bandages. For the most part this constituted a satisfactory method. The original dressing was left intact for 4 to 5 days at which time it was found that in most animals granulation tissue was present and the skin edges were firmly adherent to the underlying subcutaneous tissue so that the size of the area did not vary with movement of the skin.

At this point measurement of the wound areas was performed by the method described by Carrel; i.e., cellophane tracings were made and transferred to white paper, and these areas were then measured with a planimeter and expressed in square centimeters. Inevitably the wounds were of different size at this stage, there being a 2 to 50 per cent difference. In every instance the larger area was used as the "treated" side and the smaller as the control. After the initial period, treatment was carried out every 2d day as follows: Saturated Dakin's packs were applied for 5 to 10 minutes to both wounds on each animal and the residual solution was then washed off with copious amounts of saline. On the larger or "treated" side a gauze sponge saturated with tissue extract was applied and on the control area, a saturated saline sponge was used. Both wet dressings were covered with sterile cellophane so as to prevent leakage and the outer dressing was secured. Measurements were taken of the change of size of each wound until healing had occurred. Contralateral wounds were plotted on graph paper with the abscissa measur-

TABLE I.—EXPERIMENTAL RESULTS

No. of Dog	Healing time in days of experimental wounds	Healing time in days of control wounds
2264	13	22
2266	16	26
2289	13	22
2294	16	25
2296	29	42
2315	21	31
2319	20	26
2325	17	30

Fig. 2. From the case of A. W., wound (a), showing the actual healing time and the expected healing time (DuNouy, broken line).

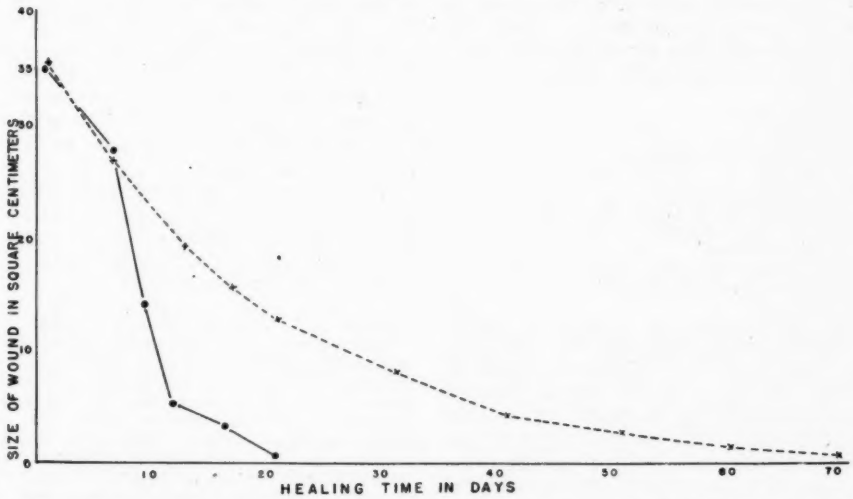

Fig. 3. Case of A. W., wound (b). This is a graph comparing the actual healing time (black curve) with the expected healing time (DuNouy, broken line).

ing time and the ordinate the size of the wounds. Ten dogs or 20 wounds were so treated.

Results. (Fig. 1.) Of the 10 animals, 2 died in the course of treatment from ruptured tracheae, following a dogfight. However, significant results were obtained before they were lost to the experiment. Eight animals, or 16 wounds, were followed to complete healing, and in every instance the treated side was healed before the control regardless of how much larger the latter was at the onset of treatment. Expressed in percentage, the treated sides healed on an average of 40 per cent faster than the controls. In the 2 animals who died the treated sides were respectively 50 to 42 per cent smaller than the control on the last measurement although they were larger than the control at the beginning of treatment.

CLINICAL STUDY

Carrel and Hartman, in 1916, published work based on observations in man and animals in which they pointed out that the healing of wounds followed a very definite pattern, with the rate of cicatrization being geometric in character, readily

Fig. 4. Graph depicting the healing progress of M. K. Black line represents the actual healing time and the broken line the expected healing time (DuNouy).

expressed by a graph-curve with time shown in the abscissa and size in the ordinate. DuNouy, in 1916 (7, 8), showed that the above curve could be expressed by a mathematical formula:

$$S' = S\,[1 - i(t + \sqrt{T + t})]$$

or

$$S' = S\,[1 - i(t + \sqrt{nt})]$$ (If t is constant)

S' = area t days later
S = wound area at a known time
T = age of wound from time of first observation S
t = time between measurements
n = number of time periods
i = a fixed coefficient which depends on the size of the wound and the age of the patient

He further showed that the i coefficient can be found when the size of the wound and the age of patients are known, but his appended table of calculated coefficients is worked out for patients only up to and including 40 years. The clinical value of his work becomes apparent when various substances are to be tested for their ability to influence wound healing; in fact DuNouy's curve of expected healing time may represent a suitable control for comparing the rate of repair of wounds in man and the influence of any growth promoting substance in accelerating wound healing. It should be remembered that the wounds on which both Carrel's and DuNouy's work was based were kept as bacteria free as possible and the subjects were presumably young, and free of underlying disease such as circulatory disturbances, diabetes, and nutritional disturbances.

Fig. 5. Case of D. R. Black curve shows actual healing time and broken line the expected healing time (DuNouy).

By use of the above formula to determine the expected course of healing and healing time, a total of 9 patients and 11 wounds were examined, treated, and followed to complete healing. A brief résumé of each case is presented.

Case 1. S. G., a 37 year old male, developed a varicose ulcer of the ankle over the external malleolus following longstanding phlebitis. The ulcer failed to improve with bed rest and the application of Unna's paste boots. The patient was treated by the application of adult tissue extract and the ulcer was healed in 30 days. The expected healing time from DuNouy's formula was 40 days.

Case 2. J. T., 33 year old male, developed 2 ulcers on the plantar surface of the right foot following x-ray therapy for calluses. Débridement was carried out and 2 cavities 6.7 and 8.2 square centimeters extending to the periosteum were left. Following the use of tissue extract applied 3 times daily in the form of wet dressings the areas were healed in 16 and 21 days, respectively. The expected healing time (DuNouy) was 14 and 21 days.

Case 3. A. W., 55 year old male, had bilateral varicose ulcers measuring 25.4 and 21.7 square centimeters. He was treated with moist dressing of tissue extract while on bed rest. Healing time: 21 and 13 days. Expected healing time (DuNouy) 70 and 48 days (Figs. 2 and 3).

Case 4. E. J., 49 year old female, had an infected granulating wound measuring 35 square centimeters resulting from a Thiersch graft failure following radical mastectomy. She was treated as an ambulatory patient having wet dressing of tissue extract applied every day for 2 weeks and every other day for the remainder of treatment. Healing time: 38 days. Expected healing time (DuNouy): 70 days.

Case 5. M. K., 50 year old female, had an abscess of the buttock which was incised and drained and an open

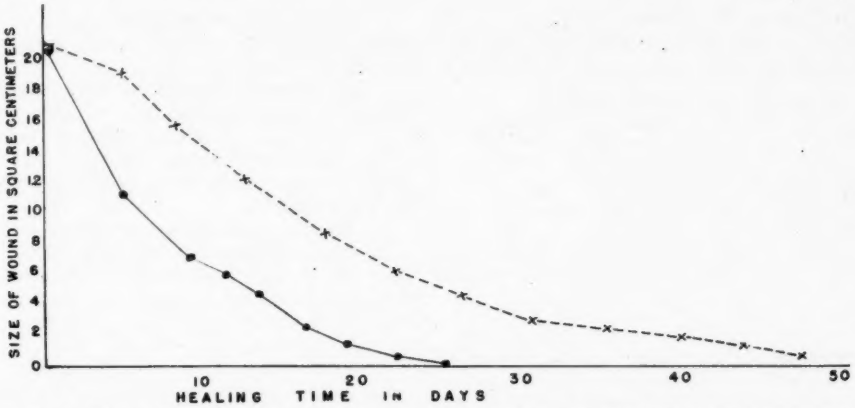

Fig. 6. Case of F. H. Solid line shows the actual curve of healing, and the broken line the expected healing course (DuNouy).

cavity 9.6 square centimeters and 8 millimeters deep was left. This was packed every other day with tissue extract gauze. Healing time: 17 days. Expected healing time (DuNouy): 28 days (Fig. 4).

CASE 6. D. R., 52 year old female, had incision and drainage of a small abscess in the left axilla. The cavity measured 2.7 square centimeters on the surface and 1.5 centimeters in depth. It was packed with tissue extract gauze every day. Healing time: 6 days. Expected healing time (DuNouy): 15 days (Fig. 5).

CASE 7. F. H., 71 year old female, had a wound separation following radical mastectomy which measured 23.1 square centimeters. Every other day fresh applications of tissue extract were applied. Healing time: 25 days. Expected healing time (DuNouy): 46 days (Fig. 6).

CASE 8. E. K., 38 year old female, had a traumatic avulsion of the skin over the dorsum of her hand. She was treated for 3 weeks with bland ointments with little healing progress. Following the application of tissue extract every other day this 11.6 square centimeter area was healed in 12 days. Expected healing time (DuNouy): 30 days (Fig. 7).

CASE 9. M. S., 52 year old ambulatory male with Buerger's disease, had an open lesion on his toe measuring 2 square centimeters. This had been completely refractory to all local treatment for 11 months. Tissue extract was applied several times a week for a period of 79 days at which time the lesion was healed.

Treatment of all the cases given was carried out as follows: At each time of treatment, Dakin's solution was applied to the wound for approximately 10 minutes, and then copious amounts of saline solution were used to flush out any traces of chlorine. Following this, gauze sponges saturated with tissue extract were applied to the wound, and covered with cellophane and suitably bandaged.

Results. Curves of the healing progress of wounds were plotted on graphs in which control curves calculated from the formula given were also drawn (Figs. 2, 3, 4, 5, 6, 7). Eight of the treated areas or 80 per cent were unequivocally healed much before the expected healing time of

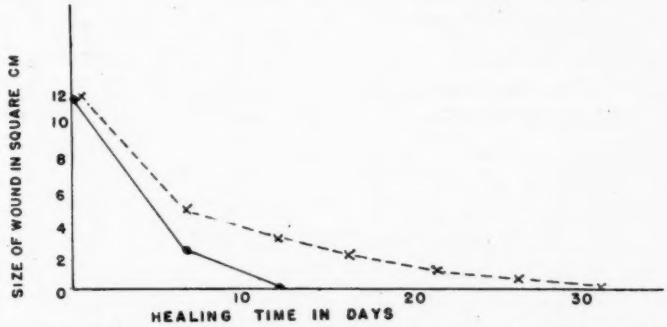

Fig. 7. Case of E. K. Solid line shows the actual curve of healing and the broken line the expected healing curve (DuNouy).

the control curve. Of the remaining 2, 1 wound was healed in the same time and 1 in a slightly longer period than the control.

TABLE II.—CLINICAL RESULTS

Patient	Actual healing time in days	Expected healing time in days
S. G.	30	40
J. T. (a)	16	14
J. T. (b)	21	21
A. W. (a)	21	70
A. W. (b)	13	48
E. J.	38	70
M. K.	17	28
D. R.	6	15
F. H.	25	46
E. K.	12	30

In evaluating these results, some emphasis should be placed on the fact that the coefficient *i* as used in the DuNouy formula had been calculated by him for patients only up to the age of 40 years. In calculating the control for 6 of the wounds shown in Table II, the coefficient *i* for 40 years of age was used despite the fact that the patients ranged from 48 to 70 years of age. Further, in 3 patients, (A. W., S. G., J. T.) underlying circulatory disturbances were present. In the 2d case (J. T.), ulcers were the result of x-ray therapy for calluses, and the wounds on the plantar surface of the foot, following excision and débridement, extended to the phalangeal heads. Covering of the exposed bone required a major portion of the healing time.

It should also be pointed out that the presence or absence of infection, the degree of contamination, and possibly the type of invading bacteria have a definite effect on the efficacy of the extract and hence on the healing of a wound. These observations were made in both animal and clinical cases since, when gross infection was present, the wound remained stationary in size until the infection was controlled. Similar observations were made by Carrel. The presence of certain bacteria probably destroys the action of tissue extract.

SUMMARY AND CONCLUSIONS

1. Previous work with the use of tissue extract in the treatment of wounds is reviewed.

2. Some facts concerning the nature of the cell growth promoting action of adult animal tissue extract are discussed.

3. Experiments carried out on 10 dogs with bilateral wounds are described, with a suggestion as to a satisfactory type of dressing for treating wounds in active animals. Results showed that wounds treated with tissue extract healed faster than the controls.

4. Eleven clinical wounds favorably treated with tissue extract are reported. The healing time for 8 out of 10 lesions was significantly shorter than the expected healing time for normal wounds of similar size when calculated by the DuNouy formula.

5. Further clinical work is in progress at the present time, as well as studies to determine the nature of the growth promoting principles in animal tissues.

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CLASSIFICATION OF CHRONIC CYSTIC MASTITIS

A LAMENTABLE state of confusion exists among surgeons and pathologists alike as to views and classification of chronic cystic mastitis. The inconsistencies and variables in the disease are largely responsible for this lack of agreement, but all must agree that assimilation of knowledge which would eliminate needless operations and dictate correct surgical procedures, when operation is indicated, would obviously be highly desirable. During the years when there has been so much disagreement and confusion in our conception of chronic cystic mastitis, one very important point, however, has been clarified, namely, the relationship of chronic cystic mastititis to cancer of the breast. With practically no exceptions, all writers (surgeons or pathologists) who have offered their opinion on this subject during the past several years have expressed their firm belief that cancer may and does develop in areas of chronic cystic mastitis even though there is as yet no means of determining just how often and in what types of chronic cystic mastitis this may occur. However, the mere establishment of this relationship as a fact paves the way to a more accurate understanding of the various types of lesions. In our opinion[1], any conception or classification of chronic cystic mastitis must therefore correlate pathologic with surgical knowledge and likewise attempt to identify the type of lesions which might develop into cancer. Complete fulfillment of this last ambition will naturally be very difficult to realize, chiefly because a vast majority of lesions exhibiting the nodularity of chronic cystic mastitis are excised, thereby not allowing us to determine just how many might have developed cancer and at what date. Moreover, even though we may have observed cancer develop in a breast which was the site of chronic cystic mastitis, we will have had the opportunity to know what type was responsible for the malignant change only when we had performed biopsy or incomplete removal months or years previously. Such situations develop or are created only occasionally, and correctly so. Nevertheless sufficient facts are now apparently available to allow the development of a more satisfactory classification, which is herein described. Introduction of new terms is carefully avoided, since they frequently add confusion; old familiar terms are used and an attempt is made to adhere closely to their definition.

Before a pathologic classification of any given disease can be attempted, the various changes observed in the different types of that disease must be reviewed and analyzed. A

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study of numerous specimens of chronic cystic mastitis reveals 5 or 6 major histologic features; at times, 2, 3 or more of these may be observed in a single section, but with few exceptions one of these pathologic changes will predominate. *Fibrosis* is encountered in practically all specimens; in some it is so pronounced that the glandular elements may have been displaced to a pronounced degree. *Hyperplasia* of the glandular elements is perhaps the next most common change observed. This hyperplasia may affect the glands themselves, or the ducts; usually if one structure is increased in number, the other will be also, but not necessarily so. The hyperplasia usually takes place in an orderly fashion with little or no change in cellular characteristics although dilatation of the ducts or glands is commonly observed. Not infrequently the hyperplasia develops with changes which are of a *precancerous* nature, i.e., there is much variation in size and shape of the cells. The cells may be markedly increased in number,—layered or plicated; their nuclei are much larger and darker (hyperchromatic). As stated, there may be a variable degree of *dilatation of the ducts or glands*, particularly the former. On certain occasions, these cyst-like spaces may attain a size several centimeters in diameter, when they are designated as *cysts*. Throughout certain sections *lymphocytic infiltration* is noted to a variable degree, but no significance can be ascribed to this change. While factors in pathogenesis are not here discussed, it should be noted that endocrine imbalance is probably the most important known agent involved. When the pathologic changes here described are correlated with the clinical findings, the following four distinct classifications may be identified:

1. *Adenofibrosis.* In this lesion the predominant change is fibrosis. Glandular elements are present in decreased numbers; occasionally they have been crowded so much by the deposition of fibrous tissue or have become so atrophied that only an occasional distorted gland is seen. Likewise, the ducts are usually fewer in number; cystic dilatation is uncommon and is not considered a part of this lesion. Grossly the breast is firm but resilient, the glandular elements are so sparse that the cut surface is fairly homogeneous and presents an ivory white surface because of the density of the fibrous tissue. Clinically the breast is felt usually as a disc-shaped, indurated organ, although the firmness may be limited to one quadrant. The surface may be slightly roughened; rarely are there present solitary nodules of significant size. Tenderness is slight as is also pain. Adenofibrosis was encountered in 22 per cent of our cases. The average age was 37.4 years.

2. *Benign parenchymatous hyperplasia.* The predominant microscopic feature of this lesion is a proliferation of the ducts, glands, and connective tissue stroma, particularly the ducts. Considerable epithelial and secretory débris will be found in the dilated ducts and glands. The epithelial changes are limited to an increase in number—with layering and occasional plication. Hyperplasia may be found but no neoplasia. Occasionally the hyperplasia involves primarily the glands, which overrun the microscopic field; we apply the term *adenosis* to such lesions since by definition no other term appears more appropriate. The increase in connective tissue is variable but is never as pronounced as in adenofibrosis. Gross examination or palpation of the breast reveals numerous nodules, varying from 5 to 15 millimeters in diameter. These nodules are firm but resilient. Occasionally cord-like structures representing indurated ducts are found. No hard friable areas are found. On cut section the larger ones contain material which may vary in color and consistency from thin

amber colored fluid to thick, yellow brown, pasty material. In our series, 46 per cent of the cases were classified in this group; the average age of the patients was 43.7 years.

3. *Precancerous hyperplasia.* The hyperplasia in this group resembles that seen in cancer. There is considerable variation in size and shape of the cells. The nuclei are hyperchromatic. The cells are layered and plicated, forming numerous papillary processes. Mitoses are common. Some of the ducts may be completely filled with epithelial cells. Even though cellular activity is pronounced, nowhere is there evidence of invasion or of the breaking through of normal barriers. The lesion cannot be classified as possessing permanent benignity, nor can it be considered malignant, even though development of cancer appears possible or even probable. Palpation of the breast in such cases will reveal no characteristics different from those described under benign parenchymatous hyperplasia; in other words, there is no way to differentiate the two groups clinically. On cut section occasional small hard areas, with occasional papillary formation may be found. As in benign parenchymatous hyperplasia small cystic spaces are seen. The smaller ones contain thick, gray pink or brown exudate whereas the larger ones may contain thin, straw colored fluid. The microscopic section still remains the only mechanism of distinguishing this lesion from benign parenchymatous hyperplasia. Of the entire series 22 per cent of the cases were classified in this group; the average age was 41.6 years.

4. *Cystic disease.* In this type of lesion the cystic spaces may attain a size equal to 4 to 6 centimeters in diameter; they may occur singly but are usually multiple. In this group are classified the blue-domed cysts of Bloodgood. Fluid in the cyst is usually thin, straw colored or brown, and frequently cloudy. A variable amount of connective tissue is present between the cysts. The cysts are usually palpated as firm, smooth tumors but occasionally are mildly fluctuant. The breast tissue itself is atrophic. The lining of the cyst is smooth. Microscopically the walls are composed largely of connective tissue and may vary considerably in thickness. There is a lining of flattened cuboidal cells; occasionally these cells may be layered and appear to be degenerating. Glandular structures are much decreased in amount. Ten per cent of our series were classified in this group; the average age was 46.6 years.

Clinical manifestations aid in the differentiation between the four different types described, but accurate identification is not possible until the microscopic sections are seen. Pain and tenderness may be present in all types, but in general is less prominent in adenofibrosis and cystic disease. Findings on palpation have already been discussed. In general a flat indurated disc-shaped breast with only slightly roughened surface is indicative of adenofibrosis; large, multiple, firm, or fluctuant nodules indicate the presence of cystic disease, whereas diffuse nodularity (nodules varying from 5 to 15 mm. in diameter) is typical of benign parenchymatous hyperplasia or precancerous hyperplasia. Seldom can differentiation of the two last named lesions be achieved without microscopic sections.

As stated, surgeons and pathologists alike now agree that chronic cystic mastitis may give rise to cancer; however, as yet there is no method of determining which types are most prone to become malignant. One of the purposes of the classification herein discussed is to attempt to determine which type of chronic cystic mastitis may become malignant. If this point were clear, we could avoid operation in certain types in which symptoms were negligible, and on the other hand might prevent

cancer by the removal of the dangerous lesion while in its early stage. From our studies it appears that a malignant lesion rarely develops in adenofibrosis and cystic disease. Both benign parenchymatous hyperplasia and precancerous hyperplasia may become malignant; the latter is much more dangerous than the former. In our opinion a great number of those lesions exhibiting precancerous hyperplasia would develop into cancer if treatment were delayed long enough. As intimated previously, an accurate estimation of the percentage probability of malignant change will never be known, since most lesions are removed surgically a short time after detection; moreover, it is impossible to tell from microscopical examination of a cancer just what type (if any) of chronic cystic mastitis existed previous to the development of the cancer. We wish to emphasize, however, that on many occasions areas of chronic cystic mastitis (one of two types of hyperplasia herein discussed) are found adjacent to cancer.

Our study has led us to the following conclusions regarding therapy. Since adenofibrosis and cystic disease rarely develop into cancer, operation need not be advised in these lesions unless symptoms are significant. Since it is impossible to distinguish benign parenchymatous hyperplasia from precancerous hyperplasia clinically, and since either may become malignant, excision will be advisable in these lesions. Excision should be liberal, a large wedge-shaped segment being removed, since dangerous areas of hyperplasia may exist in adjacent areas which are not palpable. When microscopic section reveals precancerous hyperplasia in the segment removed, we are *definitely* of the opinion that the entire breast (not including the pectoral muscles) should be removed, since the lesion is almost certainly diffuse, and if left untreated long enough, the probability of development of cancer is great. No surgical therapy is indicated in the remaining breast unless evidence of chronic cystic mastitis is present. WARREN H. COLE.

Fig. 8. Cutting the digastric and stylohyoid tendons loose from the hyoid and dividing the former to allow better exposure of the upper carotid sheath and the jugular bulb. The 11th nerve branch to the sternomastoid is cut (but the main trunk is protected) and the common facial vein is divided. (Smaller tributaries of the jugular have been omitted.)

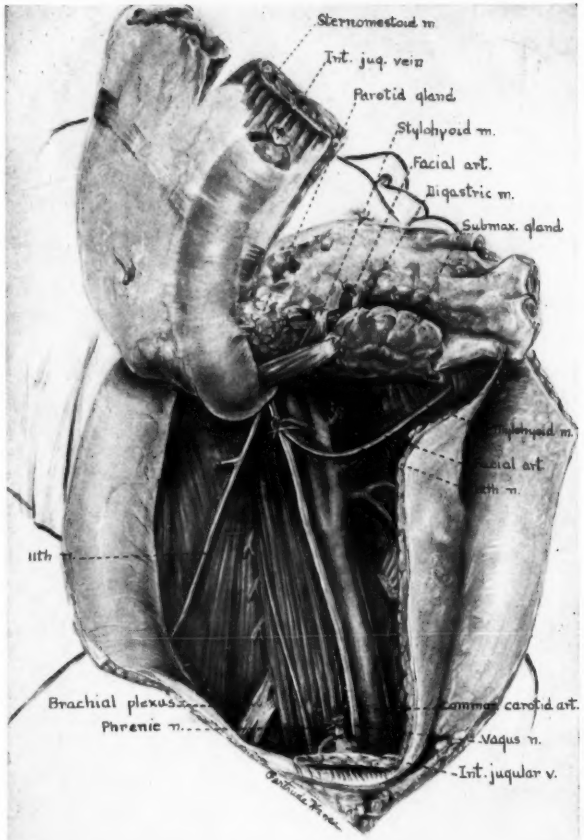

Fig. 9. Facial and occipital arteries divided. Submaxillary gland rotated up out of its fossa and the 12th nerve is preserved. Dissection continued upward on the mylohyoid muscle to the jaw. The anterior belly of the digastric may be reflected up with the specimen, or it may be excised separately, but more of the submental area should be dissected than is shown here.